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ABSTRACT

This report examines the extent and nature of marihuana use in the U.S. It presents information on the social and psychological influences as well as the toxicological and pharmacological effects. It also analyzes effects on behavior and discusses theraputic aspects of the drug. (Author/HMV)

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MARIHUANA AND HEALTH

FOURTH ANNUAL REPORT
TO THE
U.S. CONGRESS

1974

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MARIHUANA AND HEALTH

Fourth Annual Report
to the U.S. Congress
From the Secretary of
Health, Education, and Welfare
1974

National Institute on Drug Abuse
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Rockville, Maryland 20852

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Several members of the scientific community willingly undertook the task of revising and sometimes extensively rewriting an earlier draft of this Report to take into account more recent findings. They are:

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Dr. Douglas Ferraro, University of New Mexico, Albuquerque, New Mexico—Preclinical Behavioral Effects
Dr. Louis Harris, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia—Preclinical Research
Dr. Lissy Jarvik, University of California at Los Angeles—Effects of Marihuana on Chromosomes and Reproductive Processes
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Dr. Monique Braude—Preclinical Research, viz toxicological and pharmacological effects
Dr. Norman Krasnegor—Preclinical Behavioral Effects
Dr. Louise Richards and Dr. Robert Petersen with the assistance of Drs. Michael Backenheimer and Daniel Lettieri—Extent and Nature of Cannabis Use in the United States
Dr. Michael Rolnick—Therapeutic Aspects
Dr. Joseph Silvio—Effects in Man, viz chronic effects and section on cannabis and psychopathology
Dr. Stephen Szara—Effects in Man, viz acute effects and chromosomes and reproductive processes
Dr. Robert Willette—Preclinical Research on chemistry and metabolism

Dr. Robert C. Petersen as senior editor had primary responsibility for the overall preparation of the Report as well as writing the Summary.

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Introduction

It is now almost 7 years since the inauguration of a high priority HEW program to study the implications of marihuana use for the American people. In 1967-68 when the program began, research efforts were seriously hampered by the lack of standardized natural and synthetic materials, the intense controversy surrounding the topic, and varied legal and bureaucratic barriers to conducting such research. The emotional climate was far from conducive to a sober consideration of the problem. Legally, marihuana was usually classified with such seriously addictive drugs as heroin and morphine.

There have been many changes since 1968. A more thoughtful, more rational approach has largely displaced the emotionally charged atmosphere of the past. This is due in no small part to increased scientific knowledge resulting from an increased research investment. Five years ago a little over a million dollars was spent for 27 marihuana research projects being supported by a predecessor program of the present National Institute on Drug Abuse. Nearly 5 million dollars supported some 65 Institute projects last year (fiscal year 1974). This expanded research effort has greatly enlarged our understanding of cannabis use and is enabling us to better assess its hazards.

But the original concern was understandable. History bears witness to the difficulties of placing drug use, especially of new substances, in realistic perspective. Dangers have sometimes been minimized; at other times potential risks have been exaggerated. When coffee, for example, was introduced into Western Europe from the Near East much controversy arose over the possible dangers associated with its use. Penalties as extreme as death were exacted for its use. Conversely, the hazards of other drugs later proven to be dangerous have not always been obvious on initial introduction. Had cigarettes come into use at a time when their present health implications were well documented, there is little question that public health measures would have been taken to prevent or discourage their adoption and habitual use. The medical and scientific community has also not been immune from error. Heroin at the time of its first introduction was believed to be nonaddictive and was even advocated as a "cure" for morphine addiction! Cocaine was at first thought completely safe and seen as a substance with profound therapeutic implications. More recently, Thalidomide was originally believed to be an unusually safe sedative—especially for use by pregnant women—because it was thought to be unusually nontoxic and free of hangover effects. Diethylstilbestrol was the drug of choice for various gynecological and obstetrical problems, and only after several decades of use did we realize that when given to pregnant women during certain critical periods of fetal development the drug may lead to cancer development in the female offspring of those pregnancies.

It is against this backdrop of historical errors that the present concern over marihuana must be considered. Earlier reports, including that of the National Commission on Marihuana and Drug Abuse, have tried to place the health and social concerns over cannabis use into realistic perspective. Perhaps inevitably, material from these reports, often taken out of context, has been employed in polemics, and the reports have sometimes been criticized for being either "too soft" or "too hard" on marihuana. As in the past, the present Report attempts to evaluate present evidence as objectively as possible.

The original fourth edition was completed in draft form early this year before the availability of several important studies which may indicate more serious implications to cannabis use than previous research suggested. Release of that report was delayed so that these more recent studies might be included in this fourth edition and the present state of our scientific evidence placed into a more accurate perspective.

These more recent studies deal with three areas of concern. They are: effects on male sex hormone levels, interference with the body's immune response, and effects on fundamental cell metabolism. The implications of these preliminary studies are, at this point, speculative. There is concern that alteration in hormone levels as a result of chronic use may interfere with normal adolescent development or with sexual differentiation of male fetuses if cannabis is used by pregnant women at critical periods of fetal development. Effects on the immune response and on cell metabolism might seriously affect resistance to disease or result in a variety of degenerative or genetic changes. Thus far there is no clinical evidence indicative of such consequences although continuing research is obviously required.

An additional source of concern is the emergence of higher potency material such as hashish oil on the illicit market. The implications of the use of much stronger materials may be considerably more serious than use of what has typically been relatively low potency marihuana. This—combined with increasing numbers of more habitual users as well as younger adolescent users—makes present usage trends worrisome.

Whatever the ultimate evidence of more serious consequences of chronic cannabis use, there is little question that acute marihuana intoxication interferes with immediate intellectual functioning as well as with driving and other complex psychomotor skills. Thus, marihuana is not harmless, and additional research into the possible consequences of more habitual use is needed.

We must also recognize that no drug with major pharmacological action—including marihuana—can ever be truly safe. It is inevitable that further research will disclose additional hazards. In developing rational social policy, scientific evidence of a health hazard must be balanced against social and economic costs incurred by possible alternative strategies for discouraging drug abuse. We sometimes forget that rather than being restricted to our own society, drug abuse is a worldwide phenomenon. It is a problem better met with calm reason than with hysterical reaction. This report is part of a continuing effort to provide a data base for a progressively enlightened approach to this problem.

Robert L. DuPont, M.D.
Director
National Institute on Drug Abuse

Summary

Extent and Nature of Cannabis Use in the United States

The best current data indicate that approximately 1 in 7 Americans 12 years of age or older has made some use of marihuana. Although more definitive data on a nationwide sample of the general population will not be available until spring 1975, present indications are that use has not changed appreciably in the general population since it was last reported in the third *Marihuana and Health* Report.

Overall estimates of national use mask the widely varying trends and levels of use by various subgroups and by regions of the United States. For example, there is some evidence that use among high school and junior high school students continues to increase though perhaps at a slower rate than in previous years. There are also wide geographical differences in the number who have tried the drug. Almost 1 in 4 living on the west coast has used marihuana, while in the South less than 1 in 14 has done so. Studies of use in the various States also reflect wide regional variations.

A recent followup study of a nationwide sample of high school senior boys whose drug use was first explored in 1969 reveals a marked increase in the nonusers who have used since then. In 1969 only 20 percent had experimented with the drug; by 1974, over 60 percent had done so.

Adolescent drug use, like that of adults, differs markedly by geographical area. Over three times as many teenagers have used marihuana in the West as have used it in the South (23.5 percent vs. 7.0 percent).

One west coast county high school population has been of particular interest because it is an area of extensive drug use for which unusually complete trend data are available for the past 6 years (1968-74). Use has continued to increase over the 6-year period. While only a little over a quarter of the male high school freshmen in the 1968 survey had used marihuana during the previous year, almost half had done so by the time of the spring 1974 survey. Although this represents nearly a twofold increase of users in this relatively young group, it is also noteworthy that this was the first year since the survey was begun in which a slight (2.6 percent) decline was noted in the freshman age group. At the time of the first survey (1968) use by senior girls lagged significantly behind that of boys (32 percent vs. 45 percent), but by 1974 the two sexes reported having used almost equally (62 percent for boys vs. 58 percent for girls). Generally, the rate of increase in use appears to have slowed since 1971, although total use continues to increase in this high use county.

Three State surveys of general population use illustrate the marked regional differences in use patterns. In Pennsylvania 22 percent of those aged 15 or over had ever tried marihuana, while in Minnesota and South Carolina the proportions of a similarly aged sample were 12.5 percent and 7.8 percent respectively. As in other nationwide surveys, regular users made up half of those reporting having ever used.

Cannabis use by college and university students continues to be extensive, although there are marked regional variations in this age group similar to those found among high school students.

Serious doubt has been cast on the general belief that college students use marihuana to a greater extent than their noncollege attending peers.

One major followup study of young men first studied while high school students has found that use, at least during the first year following high school graduation, was virtually identical in both groups.

In the general population about half of those who have ever tried the drug are not currently using it. However, among those who have continued to use marihuana, over half do so once a week or oftener and about 1 in 5 does so on a daily basis.

New light has been shed on some of the influences involved in continuing or discontinuing marihuana use. Attitudes approving social deviance, social support for drug use, friends' approval of such use, and lack of church attendance are some of the factors predictive to some degree of marihuana use among high school students. "Openness to experience" was an important predictor of use in those not yet users. In one study, most heavy marihuana users on the college level have reported that they do not use in situations where control of behavior or concentration is required.

The most significant factors related to the cessation of marihuana use by former college users have been found to be the development of commitment to nonstudent roles, family and job constraints, and increasing social isolation from other users. Age per se was not a significant factor.

Previous editions have discussed in detail marihuana and its relationship to the use of other drugs. Prior use of alcohol and tobacco in youthful groups is closely associated with later cannabis use. Contrary to popular opinion, there is little evidence to support the contention that marihuana use displaces the use of alcohol and other drugs. Those who use marihuana are also likely to use alcohol—often simultaneously. Moreover, marihuana users as compared to nonusers are more likely to use or have used other, both licit and illicit, psychoactive drugs. The more heavily a user smokes marihuana, the greater the probability he has used or will use other drugs. It has been suggested that such use is related to "drug use proneness" and involvement in drug using subcultures rather than to the characteristics of cannabis, per se.

Preclinical Research

The preclinical findings of greatest interest and potential significance during the past 2 years have been a series of studies indicating that delta-9-THC (and possibly other marihuana constituents) has an effect upon certain basic cellular mechanisms which involve the uptake of amino acids and the nucleotides into primary nuclear components such as DNA. Since this may interfere with basic biological processes, the preliminary data raise the possibility that the effects of marihuana, under some circumstances, may be more widespread in the organism than has been previously thought. While many other substances from aspirin to antitumor agents show some of these effects, few are as fat soluble and, therefore, are retained as long in the body.

Initial studies, which will require considerable replication and followup before their significance is clear, have described possible adverse immunologic and genetic implications as well as potential therapeutic applications. While such possibilities exist, there is as yet no direct clinical evidence confirming them. No human research has been reported which demonstrates that disease resistance is significantly impaired by marihuana use; studies of possible genetic damage have thus far shown contradictory results.

Understanding of the chemistry of marihuana and of its constituents has continued to advance. While much of this knowledge is primarily of interest to the specialist, it is worth noting that many other ingredients, in addition to the principal psychoactive ingredient, delta-9-THC, may play a role in the drug's effects and its duration of action. Constituents, such as the other primary cannabinoids and metabolites, may serve to modify various aspects of the drug's action and may also have other biological roles. By better understanding the complex chemistry of marihuana's constituents we can better understand the implications of its use and the mechanisms of its effects.

Forms of liquid hashish called hashish oil have come into illicit use since the last report. Their potency, reportedly ranging from 22 to 70 percent delta-9-THC, is significantly greater than that of the usual hashish previously available (usually not greater than 10 percent delta-9-THC). Since hashish oil has not yet come into widespread use, the implications of its use have not yet been investigated. However, availability of a much stronger cannabis preparation might be expected to make adverse effects more likely.

New and improved methods for detection and quantification of marihuana and its constituents in body tissue and fluids have been an important aspect of recent developments. While many of these are quite sensitive, unfortunately they are not yet simple enough for routine medical use or inexpensive wide-scale screening. Development of simpler procedures remains an important goal which has significant research, clinical, and forensic implications.

Animal experimentation with marihuana and synthetic delta-9-THC continues to be a valuable tool in understanding possible toxic and other effects in man, the drug's interactions with other drugs, and the mechanisms of action of cannabis.

New data on the effects of marihuana on human lung explants (lung tissue grown in artificial tissue culture) continue to indicate a variety of changes in DNA synthesis, cell division, and growth. Whether such changes have implications for humans similar to those produced by tobacco smoke remains in some question. Animal studies of chronic marihuana smoke inhalation are in progress and should yield better answers to this important question.

Two aspects of delta-9-THC which have recently been investigated may prove to be of importance in future therapeutic application of the drug. There is preliminary evidence that delta-9-THC delays rejection of skin grafts in rats, which suggests a possible usefulness in organ transplant surgery. A second aspect, the inhibition of solid tumor growth in mice, may also eventually prove therapeutically useful in the treatment of human tumors. It should be reemphasized that this preclinical work is highly preliminary and that the treatment possibilities are only speculative at this time.

Previously reported anticonvulsant effects of marihuana in animals have now been corroborated by several investigators. However, this antiepileptic property of cannabinoids is nonpersistent because of tolerance development. This, coupled with the psychoactive properties of the drug, casts into doubt the potential therapeutic use of cannabis or its synthesized constituents as effective human anticonvulsant agents.

Preclinical Behavioral Effects

One interesting finding in animal behavioral studies is that marihuana (at least in short-term administration) in a variety of animal species has been found to reduce expressions of aggression. This observation is consistent with the widespread clinical impression that marihuana in humans, unlike alcohol, tends to reduce aggressive behavior rather than to potentiate it.

Animal studies to date also suggest that in order to develop behavioral tolerance to the effects of marihuana (i.e., the ability to compensate for the disruptive effects of intoxication), it is necessary for the behavior to be practiced while the animal is intoxicated. Thus, contradictory experimental findings reported in man may be partially attributable to behavioral mechanisms—learned compensatory responses while under the drug's influence—rather than pharmacological ones.

Although tolerance to many of the effects of marihuana has been convincingly demonstrated in animals and there is evidence of it in humans, dependence has not typically been found in animal experimentation. Most research has found animals reluctant to self-administer natural or synthetic material or to consume it in food or water when alternatives are available. Two groups of investigators did, however, find some evidence of physical dependence following prolonged drug administration. Since there is now some preliminary evidence of possible withdrawal symptoms following heavy use, the possibility of physical dependence will continue to be carefully investigated in further animal research.

Human Research

Acute Effects

Studies on the acute effects of marihuana and its major ingredients have continued. Such research is useful in learning the role various marihuana constituents play in producing psychological and biological effects or in modifying the effects of marihuana's more active components. Two of the most abundant cannabinoids are cannabidiol and cannabinol. Neither was found to have effects in itself, although a possible interactional role with delta-9-THC, the major psychoactive ingredient in natural marihuana, has not been ruled out. Delta-8-THC, another constituent of cannabis, has been found in human trials to have effects qualitatively similar to, though quantitatively less than, delta-9-THC. 11-hydroxy-delta-9-THC, believed to be the major metabolite of delta-9-THC, has been found to be active by three groups of investigators. The question of whether delta-9-THC acts primarily through its conversion to this metabolite has not yet been resolved. Research on the metabolic aspects of marihuana and its various constituents has helped elucidate some of the possible mechanisms of action of the drug. These data will also be useful in anticipating and explicating possible interactive effects of cannabis with other commonly ingested drugs.

One report on the effect of marihuana ingestion on the electrocardiograms of a small sample of young men expressed concern about possible effects on heart action, both acutely and on a cumulative basis. However, the observed effects were not replicated in a second study and may represent a benign, temporary stimulating effect of the drug rather than any seriously adverse effect on cardiac function; further clarification is required. Previous *Marihuana and Health* Reports have expressed concern that the effects of marihuana—thus far explored principally in relatively young adults—might be of greater consequence in older, less healthy groups. At least one study of patients with clearly established coronary artery disease has found that chest pain (angina pectoris) was exerienced sooner after exercise and after less work while smoking marihuana than while smoking an inactive placebo. Thus use of marihuana by those with coronary difficulties may be especially unwise.

Another study testing whether marihuana can alter physiological response to stress found that with moderately high doses response to experimentally induced stress was not reduced.

Several investigations of the acute effects of marihuana on brain electrical activity have been conducted. These electroencephalographic studies tend to provide objective support to users' assertions that, when intoxicated, they tend to selectively attend to particular aspects of the outside world. Alcohol, by contrast, was interpreted as having a generalized suppressive effect on brain arousal.

A variety of studies further confirms the fact that marihuana impairs short-term memory processes while the user is intoxicated. This impairment appears to involve the transfer of information from short-term memory to longer term memory storage.

Because of domestic restrictions on research involving the experimental administration of cannabis to women, there has not been systematic comparison of effects on males and females in the United States. However, Canadian investigators—employing a wide range of intellectual and psychomotor tasks—have found few differences between the sexes in their performance under conditions of acute intoxication.

Cannabis and Driving

Evidence that marihuana has a detrimental effect on driving performance, especially as the dose increases, continues to mount. It has been found to increase both braking and starting times, to adversely affect attention and concentration abilities, and to detract from performance on a divided attention task, all of which are presumably involved in driving. A recent Canadian study of driving ability examined the performance of marihuana-intoxicated drivers under both driving course and actual traffic conditions. A significant decline in performance as measured by several criteria was found in most drivers tested. Based on the accumulated evidence, it seems clear that driving while under the influence of marihuana is ill-advised.

Genetic and Reproductive Aspects

The third report on *Marihuana and Health* indicated that "there continues to be little evidence from human case reports and research studies that cannabis preparations have either a significant teratogenic effect or have any significant effect on chromosome breakage." In one more recent study of marihuana users an increase in chromosomal abnormalities was found while in another study utilizing known dosages of pure cannabis preparations no drug-related increase was found. These contradictory data may reflect methodological and sampling differences, and considerable uncertainty exists regarding the possible significance of these chromosome breaks. Hopefully, the present uncertainty will be clarified by ongoing or newly designed studies such as those looking at chromosomal number and DNA metabolism.

Chronic Effects

While tolerance to the effects of marihuana has not been generally observed among American users, there is increasingly convincing evidence that tolerance (i.e., larger dosages required to produce the same effects originally found with lower dosages) does develop under conditions of heavy, regular use. Given the relatively low doses and infrequent use typical of present patterns of use in the United States, it is not surprising that tolerance has not usually been observed. One report based on a study of subjects in a hospital setting (receiving relatively large amounts of THC) describes an abstinence syndrome occurring following abrupt withdrawal of the drug. This withdrawal syndrome is reportedly characterized by sleep loss and disturbance, irritability, restlessness, hyperactivity, decreased appetite, sweating, sudden weight loss, increased salivation, and increased intraocular pressure. While the amounts involved were usually large and quite atypical of current use patterns, the possibility of a withdrawal syndrome in at least some American heavy users must be considered.

Preliminary evidence in one study of chronic American marihuana smokers indicates that levels of the male hormone testosterone may be lowered in chronic users. This study reported that 6 of the 20 young men studied had reduced evidence of fertility (lowered sperm counts), and 2 were impotent. Testosterone levels in this group were significantly lowered, though they remained within what are generally regarded as normal limits, and promptly increased upon discontinuing marihuana use. Preliminary findings from two other studies of young male subjects were inconsistent: one found a depression in serum testosterone levels, another did not. The significance and implications of these findings will require further study. It has been speculated that depressed testosterone levels in young boys may affect adolescent development, or that marihuana consumed regularly during early pregnancy—while sexual differentiation is occurring in the male fetus—may adversely affect its development. There is, however, no empirical evidence to this effect at present.

The possibility that regular, heavy doses of marihuana may result in a diabetic-like response has been suggested by preliminary research, but it is quite tentative and requires further investigation. There is no clinical evidence as yet of marihuana-precipitated diabetes.

While chronic users in the United States have used for appreciably shorter periods of time than users overseas, studies of American chronic users are potentially of great importance in assessing possible implications of marihuana use for the American population. In one large-scale study of undergraduate student use comparisons were made between nonusers (including those who had done a limited amount of experimentation), occasional users, and chronic users (those who had used three or more times a week for 3 years or more or for 2 years if use was almost daily). No statistical differences in academic performance were found nor was there any evidence of reduced motivation. It should, of course, be noted that some chronic users who dropped out may have been excluded. As yet, however, there is no evidence that in a college population use is typically accompanied by impaired performance or motivation. Another study of moderately using medical students who had used regularly for 3 or more years and who were matched with nonusing medical students for intelligence found no difference on an extensive battery of neuropsychological tests.

It should be kept firmly in mind that most research on American users involves samples of motivated groups using only modest amounts of cannabis (by overseas standards) for limited periods of time. Overseas studies of longer term, heavier using groups have been limited to small samples. Rarer consequences of use or more subtle impairment which may be significant in a highly urbanized, industrial society may have escaped detection in these agrarian cultures.

Cannabis and Psychopathology

To date, well-controlled studies demonstr[illegible] few differences in psychopathology in carefully matched samples of users and nonusers. However, a series of clinical and case reports associating marihuana use with a wide range of psychiatric symptomatology has appeared. The question of a causal role of cannabis still remains largely unresolved. Most such studies have reported on small self-selected samples, many of whom were consuming other drugs in addition to marihuana. Previously reported (cf. earlier editions of *Marihuana and Health*), larger scale studies in countries where cannabis use is endemic which have described intellectual deficit or psychopathology associated with cannabis use have been poorly controlled, confounded by multiple drug use, and used dubious diagnostic methods. Observations made in the last Report continue to appear sound. Serious psychiatric complications of use seem to be most common in those with a previous history of psychopathology who consume large doses of cannabis or inadvertently overdose. More recent findings tend to confirm the observation that American marihuana users who use heavily are somewhat more likely to come from populations with a higher preexisting risk for psychiatric problems than has the general population.

Therapeutic Aspects

Cannabis has had a long history of use in native medicine to the present day, and in Western scientifically based medicine until supplanted by other more uniform and/or convenient drugs. More recently, with its investigation as a drug of abuse, has come a renewed interest in it and its synthesized constituents for use in modern medicine. It is too early to know which of the several applications that are being made of the drug might prove to be ultimately useful. While cannabis is a drug of very low toxicity, it has, at the same time, limitations due to the psychological effects and possible tolerance to its effects developing over time.

A preliminary study of the possible therapeutic use of marihuana has explored several possible facets of the action of THC with a group of cancer patients. This preliminary work suggests that THC may be valuable in reducing the need for other pain-reducing drugs in acting as an antiemetic, in retarding weight loss, and for its tranquilizing and mild mood-elevating properties. Whether these initially observed effects will prove useful over more extended periods of use with larger numbers of patients is not known at this time. It is, however, reported that the side effect of intoxication sought by street users was not troublesome—it was not experienced by the patient sample studied. The researchers interpret this as an indication of the importance of personal expectation (the "set" of the user) in determining one's subjective response. It is noteworthy that Jamaicans who use the drug primarily as a work adjunct and to relieve the discomfort of arduous conditions also do not characteristically report the "high" sought by American recreational users.

Other investigations have studied the use of cannabis or its constituents for such diverse purposes as the treatment of glaucoma and asthma, as a sedative, as a possible analgesic, as an anticonvulsant, and as an antidepressant. While preliminary findings in the treatment of glaucoma and asthma have been encouraging, further clinical trials are needed, and the drug's usefulness may be limited by several factors including the development of tolerance to its effects. Some investigators report that breathing efficiency assessed by measures other than bronchodilation is actually impaired. This finding also casts doubt on the clinical usefulness of marihuana in treating asthmatics. The drug's sedative potential is questionable because of its interference with normal sleep patterns, some "hangover" effects and mild insomnia following its discontinuance. Recent animal research, while confirming the antiepileptic property of the drug in short-term use, suggests that the effect is nonpersistent unless the dosage is increased over time. Results to date have shown no indication of effectiveness in the treatment of more seriously depressed patients. Finally, recent animal research discussed elsewhere (cf. Preclinical Research) raises the possibility that marihuana may have some usefulness in facilitating organ transplants and in the treatment of some types of tumors.

1 Extent and Nature of Cannabis Use in the United States

Three previous editions of *Marihuana and Health* have reported in some detail on the extent and patterns of marihuana use and on the social and personal characteristics of American users (25, 26, 27). Summaries of the data from nationwide studies as well as surveys of various subgroups within the general population can be found in those editions along with findings concerning drug histories, lifestyle, parental and peer influences, personality, and some aspects of drug selling associated with cannabis use. In the current report, more recent figures on use in the United States are discussed together with new patterns and trends in youthful drug use. Recent findings that throw light on previously unexplored aspects of cannabis use are also reported. This is not, however, a comprehensive review of the epidemiology of cannibis use. Previous reports should be consulted for a more comprehensive account of the area.

Present Patterns and Changes in Use

A more definitive indication of 1974 nationwide trends must await completion of a study of the general population now being conducted under the aegis of the National Institute on Drug Abuse. This survey of the general population will be completed by spring 1975. While there is little evidence thus far of marked changes in use among the general population, there are indications of continued increases in use by children, teenagers, and young adults. Of course, significant changes in one group's usage may not markedly alter overall rates.

The most comprehensive figures on nationwide drug use through 1972 were those obtained by the National Commission on Marihuana and Drug Abuse (29, 30). The Commission's last nationwide survey, conducted in late 1972, indicated that marihuana use had continued at almost the same level as found in 1971.[1] The overall "ever used" figures for the 2 years were:

Proportions Who Had Ever Used Marihuana*

	1971	1972
Youth (12-17 years)	14.1%	13.4%
Adults (18 years and older) . .	15.4%	14.7%

* National Commission on Marihuana and Drug Abuse.

Independently of the Commission's study, two polls were conducted in 1973. The figures obtained deviate slightly from those of the Commission but again probably reflect the statistical variation to be expected when different samples of the population are queried. The Gallup Poll reported in February 1973 that 12 percent of those 18 or older have ever used marihuana, compared with the Commission's figure of 14.7 percent (16). The 2.7 percent difference is well within the expected margin of sampling error. Columbia University's School of Public Health polled adolescents aged 12-17 in September 1973 and found 17 percent reporting that they had used marihuana one or more times (21). Although this figure was 2 percentage points higher than the two previous figures of 15 percent (22), it, too, was within the range of sampling error and fairly close to the Commission's figure of 14.7 percent for the same age group.

There is converging evidence, then, that 1973's crude rate (i.e., all those who have used marihuana at least once) is not discernibly higher than that of 1972 for the population as a whole. In a review of adolescent marihuana use nationwide in 1971 and 1972, Josephson concluded that a "plateau" probably had been reached in the 12-18 year group, though apparently not for the college-age group (see below) (22).

Among those who have "ever used" marihuana in the Commission's 1972 nationwide study, the proportions who were using "now" (within the past month) were, for both youth and adults, almost exactly half; the other half were no longer using it. Among those still using, the following proportions were found at each level of frequency:

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[1] The actual figures for 1972 were very slightly lower but may have fluctuated that much merely because of sampling variations; that is, the .7 percent decreases for both youth and adults probably do not reflect an actual diminution in drug use.

Proportions of Frequency of Current Marihuana Use, 1972*

	12-17 years old	18 years and older
More than once a day	.6%	.6%
Once a day	.7	.8
A few times a week	1.5	1.4
Once a week	1.2	1.3
2-3 times a month	1.5	1.3
Once a month or less	1.9	2.4
Total, current users	7.4%	7.8%

* National Commission on Marihuana and Drug Abuse.

It is quite obvious that over half of the current users take marihuana at least once a week.

It is always of interest to know how the crude rates differ from group to group in the population. Among those aged 12-17, in the National Commission's nationwide study, 14.3 percent of the males and 12.4 percent of the females had used marihuana (32). However, at older ages the percentage who had ever used marihuana rose significantly, from 3.2 percent at ages 12 and 13 to 28.3 percent at ages 16 and 17. Use was skewed by region of the United States with the West showing 23.5 percent use and the South 7.0 percent. These findings are basically the same as those in the nationwide study conducted 1 year earlier by the same organization (33).

A recent followup study of a nationwide sample of high school boys first studied in 1966 reflected usage trends in a young adult male population. In 1969 when this group was high school seniors (or equivalent in age), 20 percent had tried marihuana. By 1974, 5 years later, over three times as many (62 percent) had done so. By 1974, nearly four times as many as in 1969 (21 percent in 1974 compared to 6 percent in 1969) were using once a week or more often. That represents about a fifth of the entire group (19). Thus at least one significant source of data on trends in drug use suggests that the upward trend in cannabis use in this population segment is continuing. It should, of course, be kept in mind that even a marked increase in one small segment of the population may not appreciably affect overall use rates (college students, a traditionally high use group compared to all adults, for example, represent only 3 percent of the total population).

State Studies

Until relatively recently, only one study sampled marihuana use by an entire State's general population, that conducted in 1970 by the New York State Narcotics Addiction Control Commission (7). Since that time at least three statewide reports have been issued and a number of other State studies have been initiated. The three reports now available were conducted with individuals as young as 14 years and included all older age groups. In two of these studies, the usage rates were somewhat lower than the rate reported for the entire nation, even though younger respondents were included:[3] in Minnesota, the proportion 14 years and older who had ever used marihuana was 12.5 percent (8); in South Carolina, it was 7.8 percent (9). As in the nationwide study, regular users comprised half or less of all those who had ever used marihuana. In the third State study, in Pennsylvania, the reported rate was higher: 22 percent of those 15 years and older said they had used the drug at least once (36). These variations in State rates are to be expected in accordance with regional variations. The Northeastern, urban States would be expected to have higher rates than the Southeastern or Midwestern States, a trend which is borne out among the three States reported above.

Student Marihuana Use

Above, the nationwide findings on adolescents' marihuana use from the second annual survey of the U.S. general population were reported. The only nationwide longitudinal study of secondary school students has been conducted by Columbia University. Although not a strictly representative sample of U.S. secondary schools, the 30 surveyed schools included the major types of urban, suburban, and rural schools of different social composition. Data analysis from the first wave (1971) of the study showed considerable variation in the estimated marihuana usage in the panel schools (13). Marihuana use ranged from 23 percent in an all black school in a Southeastern city to 58 percent in an ethnically mixed school in a West Coast university town.

Preliminary data from a national survey of high school students conducted during the school year 1973-74 are now available. Like the Columbia University study this sample was not strictly rep-

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[3] The sampling procedures were not as rigorous in those two State studies in that a quota sample rather than a strict probability sample was employed.

San Mateo: Used Marihuana at Least Once During the Past Year

Marihuana—Males	**1968**	**1969**	**1970**	**1971**	**1972**	**1973**	**1974**
Seventh Grade	NA	10.9%	9.9%	17.6%	17.2%	20.0%	22.7%
Eighth Grade	NA	23.9	22.5	29.1	33.9	34.3	37.7
Freshman	26.8%	34.9	34.1	44.5	43.9	51.2	[illegible]
Sophomore	32.3	41.7	44.9	49.7	51.9	56.1	57.3
Junior	36.9	45.5	48.9	57.9	58.0	58.5	59.4
Senior	44.6	50.1	50.9	58.6	60.8	61.0	61.9
Marihuana—Females							
Seventh Grade	NA	10.7%	12.6%	12.6%	13.2%	15.0%	18.0%
Eighth Grade	NA	21.8	25.8	26.4	29.2	31.5	33.3
Freshman	22.9%	31.9	31.9	40.5	39.0	47.0	47.8
Sophomore	28.1	35.5	42.1	48.1	49.3	51.9	54.6
Junior	31.7	38.3	42.6	50.2	52.4	55.3	56.7
Senior	31.9	38.1	48.4	48.3	53.0	57.2	58.2

resentative of the U.S. secondary school population. Nevertheless, considerable effort was expended to obtain data from a wide range of schools throughout the United States. Half of the sample had, at some point, tried marihuana with about 1 in 5 continuing to use on a weekly or more frequent basis. Only 3 percent of the sample reported daily use of marihuana or hashish (4).

A nationwide study of male high school students found that those students who use marihuana—contrary to popular belief—were also more likely to use alcohol and other psychoactive drugs than their nondrug using peers. It was also found that students reporting delinquent behavior were more likely to use marihuana than those not reporting such problems (20). Regular use of cigarettes has been found both in this study and in another large-scale survey of elementary, junior, and senior high school students to be associated with a higher incidence of marihuana use. In the latter research children who were regular cigarette smokers were more likely to later use marihuana than were the nonsmokers (40).

Another student survey, conducted in two phases by New York State, obtained usage trends for a variety of drugs over one academic year. Data from public secondary school students in that State were collected at the beginning and end of the 1971-72 academic year. Something less than a third (29.5 percent) indicated having used marihuana. As has been found in virtually all other surveys of high school students, however, it should be noted that use of alcohol and tobacco was far more common than that of marihuana. Illicit drug use was found to be highest among suburban adolescents (41 percent) and lowest in upstate areas (28 percent) with increasingly higher proportions having used at each successively higher age level. Whites were found to be somewhat more likely to have tried marihuana than blacks, although the differences were small. Very extensive use (60+ times) of cannabis was found to be unusual (7 percent).

Data from all student surveys continue to make clear that experimental use of marihuana is more common than is continued, regular use of the drug.

One widely cited survey of student use of drugs is the San Mateo Survey. Now in its seventh annual administration in San Mateo County, California, the latest data (1974) show that marihuana use is up slightly from 1973, though the rate of annual increase is generally not as great as before 1971 (3). The largest increase reported in the last survey was among seventh grade girls. The table above shows the rate of marihuana use by year in San Mateo. The preliminary findings in 1974 also show that male student use of marihuana, while lower than that of alcohol, is now comparable with student use of tobacco. According to the report, although marihuana use is lower than that of tobacco in grades 7-9, the gap then begins to close, and from that point on, marihuana use by males is more commonly reported at every usage level than tobacco. Girls, by contrast, consistently make greater use of tobacco.

The absolute figures from San Mateo cannot, of course, be applied to other schools or communities since they represent only one local situation.

The fact that the trend shows a small upturn should, however, be noted.

University and College Students

Evidence strongly suggests that the use of marihuana by university students at all levels—undergraduate, graduate, and professional levels—continues to be high. One study of 788 undergraduate students at a large metropolitan university found only 27 percent who had never tried marihuana (28). A study of law and medical students at a Northeastern university in the fall of 1970 showed high rates of marihuana use with 73.3 percent of the law students and 68.1 percent of the medical students having used marihuana (39). These figures are consistent with a survey of 85 medical students in California which found that 73 percent had used marihuana at least once (41). These results differ widely from a study of graduate students at a large State university in the Southeastern United States which found only 36 percent of the men and 28 percent of the women (31 percent overall) had used marihuana (35).

The third annual report of *Marihuana and Health* also reported that use of marihuana by students was continuing to increase in colleges and universities (27). In 1972 Josephson reviewed the nationwide data and commented that ". . . it is by no means clear that college-age marihuana use has stabilized" (22).

Marihuana and Treatment

Figures from the Federal Client Oriented Data Acquisition Process (CODAP), a reporting system designed to monitor federally supported drug treatment programs, are of interest with respect to marihuana use and the need for treatment. In the period from July 1973 to February 1974, 12.7 percent or nearly 8,000 of the approximately 60,000 clients admitted to treatment programs were classified as having marihuana as their primary drug of abuse. These figures are, however, difficult to interpret for several reasons: (a) They are influenced to an unknown extent by court and school referrals for administrative convenience; (b) more than half of this group reported having used several drugs rather than solely marihuana; (c) of those using marihuana only, 45 percent reported using it less than once a week, suggesting that for some their drug use served as a mode of entry into treatment for psychological or social difficulties only partially related to their drug use (31).

Social and Psychological Influences

Parent vs. Peer Influence on an Individual's Use of Marihuana

Several studies continue to support previously reported findings that peers, rather than parents, are the more important influence on an individual's use of marihuana. Moreover, peer and parental influences are synergistic; the highest rates of marihuana usage are observed among adolescents whose parents (particularly mothers) and friends are drug users (24). Related findings indicate that both of the following apply: (a) The greater the involvement with marihuana, the greater the likelihood that those with whom one associates are also marihuana users and, therefore, the more justified one is in expecting tolerance toward one's own marihuana use; and (b) the greater the involvement with marihuana, the greater the *need to perceive* others as involved, and hence the greater the likelihood to expect tolerant reactions from others (15).

Motives and Reasons for Use

Research tends to support the finding (42) that the greater the involvement with marihuana, the less the likelihood of the adolescent users' explaining it in terms of a desire to be "in fashion" or "to be a sport." Furthermore, the more involved with marihuana, the less likely the user is to explain this involvement as being due to difficulties and the greater the likelihood of his perceiving usage in positive terms, such as a desire "to feel happy" and "to feel free." Boredom appears to be the only negative reason which users are willing to accept. While careful research studies have documented the strong influence of peer and group pressures on marihuana use, many adolescent users are somewhat reluctant to accept the view that their behavior is a function of group pressures. It is suggested that for the adolescent user to admit that his marihuana use is prompted by difficulties is to admit to a certain weakness and inability to cope with life (42). Other evidence supports this explanation; for example, it has been found that marihuana use correlates positively with low self-esteem and high experience seeking (2).

In summarizing the various motives and reasons for use, 12 factors or hypotheses recur (12, 34) in the current literature: (a) curiosity and experience seeking (38); (b) imitation and peer influences; (c) attainment of a state of well-being, "to feel better or happy"; (d) instant achievement; (e) relaxation; (f) recreation or to facilitate social interaction and avoid boredom; (g) for psychological support to deal with pain and discomfort, real or imagined, due to physical, psychological, social, or vocational conditions; (h) rebellion and juvenile waywardness as in-group mores (14) or for rejection of parental values; (i) insight or identity or search for purpose or as a way of organizing experience (11); (j) mystical-religious; (k) aphrodisiac; (l) a type of adaptive lifestyle wherein contemporary youth are in parallel pursuit of "instantness" or "instant results" as a response to a society at large which presumably favors such goals (37).

Personality Variables as Predictors of Marihuana Use

Numerous studies have described various characteristics of the marihuana user. A basic issue has been to what extent personality variables are predictive of potential marihuana use in a group of current nonusers. In an important study (18) on differentiating user and nonuser high school age groups, it was found possible to predict which nonusers would go on to use marihuana. Some of the results indicated that initiation of marihuana use was predictable in both male and female high school students by such variables as: attitudes approving deviance, lack of religious participation and involvement, social support for drug use, friends' approval of use, deviant behavior, and more intensive petting behavior. Another study (43) characterized "openness to experience" as an important predictor of future drug use in present nonusers. An empirical test (1) of the predictability of marihuana smoking found that individual verbal attitudes and reference group expectations were good predictive variables. In those instances where individual predispositions matched situational sets, prediction of marihuana experimentation was very accurate.

Cessation of Marihuana Use

Several studies have focused on the processes by which individuals terminate marihuana use. One study (5) examined college students from their school years to 2 years after graduation. This study of alumni was concordant with prior surveys of students in its finding that marihuana use predominantly reflected diffusion of an expressive student subculture. Those who stopped using marihuana did so primarily as a result of acquiring commitment to nonstudent roles and becoming socially isolated from marihuana users, although they did *not* lose all the values and norms distinctive of the student subculture. The research concluded that family and job constraints and change of associates after graduation fostered cessation of use more often than complete change from the other values of this subculture. Related work (17) has shown that the significant status changes of marriage and entry into parenthood, and not aging per se, account for former students' terminating use in their middle to late twenties. In studying circumstances in which avowed heavily using collegians said they would not smoke marihuana, one study (11) found that most would not smoke marihuana in situations where control of behavior, concentration, or emotion was required, such as when "studying" or when "under pressure, obligation, or responsibility."

References

1. Albrecht, A.L. Verbal attitudes and significant other's expectations as predictors of marihuana use. *Sociology and Social Research*, 57(2):196-207, 1973.
2. Baskett, G.D., and Nysewander, R.W. Drug use correlates. *Psychology: A Journal of Human Behavior*, 10(1):54-66, 1973.
3. Blackford, L. *Surveillance of Student Drug Use, San Mateo County, California*. NIMH Grant DA 00094, San Mateo County, California, July 16, 1974.
4. Block, R. *Self-Administered High School Study of Drugs*. Contract HSM-42-72-137, 1973.
5. Brown, J.W., *et al.* Turning off: Cessation of marijuana use after college. *Social Problems*, 21(4):527-538, 1974.
6. Caven, S. The class structure of hippie society. *Urban Life and Culture*, 1(3):211-238, 1972.
7. Chambers, C. *An Assessment of Drug Use in the General Population*. Special Report No. 1, Drug Use in New York State. New York: New York Narcotic Addiction Control Commission, May 1971.
8. Chambers, C.; Inciardi, J.; and Siegal, H. *An Assessment of the Incidence and Prevalence of Drug and Alcohol Use Within the General Population of the State of Minnesota*. Washington, D. C.: Resource Planning Corporation, April 1973.
9. Chambers, C.; Inciardi, J.; and Siegal, H. *An Assessment of the Incidence and Prevalence of Drug and Alcohol Use Within the General Population of the State of South Carolina*. Washington, D.C.: Resource Planning Corporation, August 1973.
10. Cheek, F. E. *Studies of Illicit LSD Use*. NIMH Grant MH 13746, Princeton, N.J.: Bureau of Research in Neurology and Psychiatry.
11. Cheek, F.E., *et al.* Four patterns of campus marihuana use: Part I, drug use. *The International Journal of the Addictions*, 8(1):13-31, 1973.
12. Dohner, V.A. Motives for drug use: Adult and adolescent. *Psychosomatics*, 8(5):317-324, 1972.

13. Elinson, J. *A Study of Teen Age Drug Behavior.* NIMH Grant DA 00043, Progress Report, New York. Columbia University School of Public Health, 1973.

14. Federn, E. A psycho-social view of "drug use" in adolescence. *Child Psychiatry and Human Development,* 3(1): 10-20, 1972.

15. Fisher, G. Personality characteristics ascribed to marihuana users by users and nonusers. *Behavioral Neuropsychiatry,* 4(9-10):5-12, December 1972—January 1973.

16. The Gallup Poll, *The Washington Post,* February 25, 1973.

17. Henley, J.R., and Adams, L.D. Marihuana use in post-collegiate cohorts: Correlates of use, prevalence patterns, and factors associated with cessation. *Social Problems,* 20(4):514-520, 1973.

18. Jessor, R.; Jessor, S.L.; and Finney, J. A social psychology of marihuana use: Longitudinal studies of high school and college youth. *Journal of Personality and Social Psychology,* 26(1):1-15, 1973.

19. Johnston, L. Youth in transition. Personal communication, 1974.

20. Johnston, L. *Drugs and American Youth.* Ann Arbor: Institute for Social Research, University of Michigan, 1973.

21. Josephson, E. Columbia University School of Public Health, New York, N.Y., Personal communication, December 1973.

22. Josephson, E. *Adolescent Marihuana Use, 1971-1972.* New York: School of Public Health, Columbia University, accepted for publication, 1973.

23. Kandel, D. Adolescent marihuana use: Role of parents and peers. *Science,* 181:1067-1070, 1973.

24. Kandel, D.B. *Family Process in Adolescent Drug Use.* NIMH Grant DA 00064, New York: Biometrics Research, 1973.

25. *Marihuana and Health,* Report to Congress from the Secretary, U.S. Department of Health, Education and Welfare, Washington, D.C.: U.S. Government Printing Office, 1971.

26. *Marihuana and Health,* Second Annual Report to Congress from the Secretary of Health, Education and Welfare, Washington, D.C.: U.S. Government Printing Office, 1972.

27. *Marihuana and Health,* Third Annual Report to Congress from the Secretary of Health, Education and Welfare, Washington, D.C.: U.S. Government Printing Office, 1973.

28. Martino, E., and Truss, C. Drug use and attitudes toward social and legal aspects of marihuana in a large metropolitan university. *Journal of Counseling Psychology,* 20(2):120-126, 1973.

29. National Commission on Marihuana and Drug Abuse. *Drug Use in America: Problem in Perspective.* Washington, D.C.: U.S. Government Printing Office, 1973.

30. National Commission on Marihuana and Drug Abuse. *Marihuana: A Signal of Misunderstanding.* Washington, D.C.: U.S. Government Printing Office, 1972.

31. "Quarterly Statistical Brochure." Division of Scientific and Program Information, National Institute on Drug Abuse, Alcohol, Drug Abuse and Mental Health Administration, August 1974.

32. *Drug Experience, Attitudes and Related Behavior Among Adolescents and Adults: Detailed Tabulations, Part 2C, Experience Data.* A Nationwide Study for the National Commission on Marihuana and Drug Abuse, Princeton, N.J.: Response Analysis Corporation, January 1973.

33. *Public Attitudes Toward Marihuana: Detailed Tabulations, Part 2.* A Nationwide Study of Beliefs, Information and Experience prepared for the National Commission on Marihuana and Drug Abuse, Princeton, N.J.: Response Analysis Corporation, January 1972.

34. Rollins, J., and Holder, R. Adolescent drug use and the alienation syndrome. *Journal of Drug Education,* 2(3):249-261, September 1972.

35. Rouse, B., and Ewing, J. Marihuana and other drug use by graduate and professional students. *American Journal of Psychiatry,* 129(4):415-420, October 1972.

36. Rubin, E., and Schaps, E. *A Study of Prevalence and Intensity of Drug and Alcohol Use in the Commonwealth of Pennsylvania.* Harrisburg, Pa., Governor's Council on Drug and Alcohol Abuse, Commonwealth of Pennsylvania, July 6, 1973.

37. Sebald, H. The pursuit of "instantness" in technocratic society and youth's psychedelic drug use. *Adolescence,* 7(27):343-350, 1972.

38. Segal, B. *Fantasy Patterns in College Drug and Alcohol.* NIMH Grant DA 00590, Murray, Kentucky: Murray State University.

39. Slaby, A.; Lieb, J.; and Schwartz, A. Comparative study of the psychosocial correlates of drug use among medical and law students. *Journal of Medical Education,* 47(9):717-723, September 1972.

40. Smith, G. *Drugs and Personality.* NIDA Grant DA 00065, Progress Report, 1974.

41. Solursh, L.P., et al. Attitudes of medical students toward cannabis. *Journal of the American Medical Association,* 217(10):1371-1372, September 1971.

42. Tec, N. Differential involvement with marihuana and its sociocultural context: A study of suburban youths. *The International Journal of the Addictions,* 7(4):655-669, 1972.

43. Victor, H.R.; Grossman, J.C.; and Eisenmann, R. Openness to experience and marihuana use in high school students. *Journal of Consulting and Clinical Psychology,* 41(1):78-85, 1973.

44. Winslow, T.; Hankins, R.; and Strachan, A. Drug involvement: A response to an inadequate environment. *Journal of Drug Education,* 2(3):269-278, 1972.

2 Preclinical Research

Since the third report, preclinical research on marihuana has confirmed, clarified, or, occasionally, refuted earlier data on the effects of marihuana in animals and the implications of these findings for human health.

Interest in the chemical and botanical aspects of the plant *Cannabis sativa L.* has continued. New cannabinoid acids and noncannabinoids have been isolated, and the search for nitrogenous compounds has continued. Major advances in synthesizing marihuana constituents have facilitated the production of larger quantities of delta-9-THC, the major metabolite, in addition to other radiolabeled compounds. These will be increasingly valuable for use in future biological studies. In the analytical realm, methods for routine measurement of cannabinoids in plasma and other biological media have been developed. The use of these, in conjunction with tracer techniques, has helped to unravel the complex metabolism of the cannabinoids. Study of cannabinoid acids—the major metabolites—continued in an effort to discover their biological characteristics and effects.

Data accumulated from pharmacological studies of marihuana show that the major topics of research since the last report included:

- Continuing interest in the toxicity of marihuana per se or in combination with other drugs
- Confirmation of the anticonvulsant characteristics of marihuana with acute administration, but not after chronic use
- Further elucidation of the cardiovascular properties of marihuana, especially when administered to anesthetized animals
- Interactions between marihuana and other drugs and the possible implications of polydrug use
- Effects of marihuana on the EEG, sleep, and evoked potentials
- Work on the mechanism of action of marihuana
- Additional data on a variety of chemical, pharmacological, and metabolic effects

This fourth *Marihuana and Health* Report contains a separate section to report the findings of behavioral studies on animals (see section 3 below, Preclinical Behavioral Effects) because of the large amount of research literature published in that specific area of marihuana research since the last report.

Chemistry and Metabolism

Research activity involving the chemical aspects of cannabis and its constituents continues at a rapid rate. This Report discusses only the more significant recent developments.

Drug Sources

The investigation of *Cannabis sativa L.* continued to yield new components. For instance, the biogenic precursor of delta-9-tetrahydrocannabinol —the 2-tetrahydrocannabinolic acid (THCA)—has been isolated in quantity from Mexican cannabis (38), as has the isomeric 4-acid from an Indian variant (120) and the propyl isomer— delta-9-tetrahydrocannabivarolic acid (92). Some of the minor, lower molecular weight components of cannabis resin have also been separated and partially characterized by gas chromatography (GC) and mass spectroscopy (MS) (116).

The monomethyl ether of cannabidiol (CBD) has been isolated (110), and the presence of methyl ether of cannabinol (CBN) has been demonstrated (7).

The isolation of additional noncannabinoid components continued in order to further elucidate their role in the biological effects of cannabis. For example, several of the high molecular weight hydrocarbons have been isolated (120) in addition to some phytosterols (37).

According to both technical and popular (counterculture) sources, a form of liquid hashish has appeared on the drug market. Sources indicate that it may vary in potency from 22 to 70 percent THC (4, 34, 79). This new material has been little investigated to date.

Quantities of cannabinoids for research have been made available to investigators by the National Institute on Drug Abuse. Without this service, most preclinical and human research of the effects of marihuana could not be undertaken. New syntheses of delta-9-THC have appeared, (81) and, perhaps more importantly, syntheses of the principal hydroxylated metabolites have been achieved (1, 81, 82, 97, 102). Recently the major metabolite shown to be present in man and animals, 11-delta-9-tetrahydrocannabinol-9-carboxylic acid, and the corresponding delta-8 acid have been synthesized (105, 127).

New radiolabeled cannabinoids have been prepared for essential distribution and metabolism studies. Labeled delta-8 and delta-9-THCs, with very high specific activity, have been prepared by the incorporation of tritium into the pentyl side chain (3, 127). A new carbon-14 labeled delta-9-THC has been synthesized by a more convenient route than used earlier (127). To make other derivatives available, efforts continue in chemical research.

Analytical Techniques: Detection

The development of improved methods for the detection and estimation of cannabinoids, particularly in body tissues and fluids, remains a fundamental need for all types of marihuana research. A symposium held during December 1973 considered the latest advances made in this area (86).

Gas chromatography continues to be the most frequently employed technique for identifying and analyzing cannabis constituents, as the large number of studies employing this analytical method demonstrate (30, 35, 36, 58, 78, 92, 93, 100, 116, 120-123, 126). Using currently accepted chromatographic conditions, it has been shown that the peak representing CBD also contains cannabichromene (CBC) (38, 120, 121). In recent experiments using Mexican cannabis as much as 90 percent of what had been labeled as CBD in the past was found to be CBC (120). (These findings were possible through the use of newly developed GC methods which allow the separation of CBD and CBC.) The presence of CBC will require a reevaluation of the current use of THC and CBD ratios to classify different varieties of cannabis (120). Additionally, studies indicate that the GC peak corresponding to delta-9-THC is often contaminated with cannabielsoin, the decarboxylation product of cannabielsoic acid, which is a cyclization product of cannabidiolic acid (64, 109, 121).

New thin layer chromatography (TLC) studies have appeared (14, 33, 40, 62, 103, 107). Among these, the most significant have used dansylate derivatives to determine THC in saliva up to 14 hours after marihuana or hashish has been smoked (40, 62).

A radioimmunoassay which may be applied directly to urine has been developed for delta-9-THC and its 11-hydroxy metabolite (50). Unfortunately, for use of this technique with plasma, an extraction step is required because of the extensive protein binding of the labeled THC. The first reported estimation of THC in human blood levels with a time lapse after smoking marihuana was based on the use of radiolabeled delta-9-THC in 1972 (43). Peak plasma levels of 25-50 ng/ml were indicated. More recently, a more definitive study using a gas chromatography-mass fragmentography method was reported (3). Extracts of plasma required prior purification by Sephadex chromatography. By this procedure as little as 1 ng/ml of THC in blood can be accurately determined. It was found that a peak of 19-26 ng/ml was reached 10 minutes after smoking a cigarette containing 10 mg of delta-9-THC. This level rapidly fell to 5 ng/ml within 2 hours.

The TLC method has the disadvantage that it requires a specially designed mass spectrometer. Reports using a simpler method based on derivatization and electron capture detection following gas chromatography have now appeared (36, 44). Using this method, as little as 100 ng/ml can be measured (44). A cleanup procedure utilizing high pressure liquid chromatography has also been developed. A preliminary pharmacokinetic study of the disposition of a 0.1 mg/kg (intravenous) dose of delta-9-THC in dogs indicated that there is an initial rapid distribution and metabolism phase (half-life 7.5 minutes) followed by a slow loss from the blood (apparent half-life 8 hours). This agrees with reported earlier tracer studies in humans (116).

Further improvements in the area of detection methods would allow for a more detailed understanding of the correlation among the routes of administration, metabolism, and behavioral effects.

Metabolism

To further elucidate the metabolism of the cannabinoids (66), a series of studies showed that very little of the 11-hydroxy metabolite of delta-9-THC is seen in the blood after its administration. Rather, the principal blood metabolites are the oxidation product—the 9-carboxylic acid—and a variety of side chain hydroxylated acids (127, 128). These are also the major metabolites found in urine. Several preclinical studies have identified numerous metabolites in various species. Distribution of marihuana and its metabolites has been studied by several routes of administration. It has been shown that the enterohepatic system was involved in the disposition of marihuana, when given orally (16, 31, 57, 66-68, 89, 119).

Studies to ascertain the role played by the metabolites of delta-9-THC in contributing to its pharmacologic effects were carried out by measuring various animal brain levels (29, 66, 67, 80, 128). Results obtained support the earlier belief that delta-9-THC and its hydroxylated metabolites are all active in varying degrees and collectively account for the observed effects. Further study of the individual hydroxylated metabolites continues.

Toxicological and Pharmacological Effects

Toxicity

The development of a better method for quantifying the amount of marihuana in the smoke administered to subjects contributed to more accurate evaluation of the toxicity of marihuana. In a study comparing the LD_{50} for delta-9-THC administered by three different routes (inhalation, parenteral, and oral), toxicity by smoking was equal to that obtained by the intravenous route (i.v.)—LD_{50}-40 mg/kg when the inhalation LD_{50} dose of 105.7 mg/kg was corrected for delta-9-THC losses in the rodent nasal passages. Toxicity by intragastric gavage was 20-30 times lower depending on the type of preparation used to administer the delta-9-THC (i.e., emulsion or oil solution) (104).

That the toxicity or behavioral effects of delta-9-THC are significantly related to the solvent used was also reported by others using the intraperitoneal (i.p.) and/or the subcutaneous route of administration on rodents (77, 94). In general, aqueous suspensions or emulsions in polysorbate or polyvinylpyrrolidone were found better absorbed than the oily solutions. A new formulation for i.v. administration using Emulphor, which can be sterilized and can be injected in a relatively small volume, has been found (90).

An extensive study of the physiochemical properties, solubility, and protein binding of delta-9-THC provides some clarification of these findings and has specific implications for the planning of future clinical and preclinical studies (45). The authors found that the bioavailability of delta-9-THC is influenced by a number of factors. The instability in acid solution implies that the compound may be significantly degraded in the stomach. Extremely low water solubility suggests that its solubility in plasma may be rapidly exceeded, thus producing precipitation and accumulation in a "deep compartment" (i.e., the body organs). Rapid diffusion into plastic containers and rubber stoppers and significant binding to glass necessitate careful techniques in the handling, storage, and assay of this compound in aqueous and biological fluids. Finally, the high degree of binding to the plasma lipoprotein fraction may result in large individual variability in binding dependent upon individual and species variations in lipoprotein and fat content (45).

Chronic toxicity of delta-9-THC administered orally for 180 days to Fisher rats at lower dose levels of 2, 10, and 50 mg/kg showed no morphological changes attributable to delta-9-THC. The same pattern of fighting aggression and neurotoxicity described previously after chronic administration at higher dose levels (118) occurred in this study. Tremors and clonic seizures, appearing in cyclic fashion (peaking in weeks 12, 18, and 21), were dose related; 50 percent showed seizures after 50 mg/kg, 6 percent after 10 mg/kg. Except for a rise in liver function test indices (SGOT and SGPT) suggestive of pathology in the higher dose males, clinical chemistry, hematological, and urinalysis parameters were within normal ranges. Anorexia and diminished water consumption in conjunction with a declining growth rate occurred in the second and third weeks at the high dose level but were later reversed (27).

Previously reported differences in toxicity between males and females were also found in the studies discussed above. However, the nature of these differences is inconsistent: at times females were more affected than males or vice versa (27, 118). On the other hand, pharmacological studies indicate that female rats may be more sensitive to delta-9-THC than male rats, but that testosterone or castration, respectively, can reverse this effect (24). The mechanism by which delta-9-THC produces toxicity in animals is still uncertain, but it seems to be related to the rate of absorption and the concentration of the parent compound, delta-9-THC, rather than the metabolites in the target tissues. Harbison has shown that pretreatment with phenobarbital antagonized THC induced lethality while pretreatment with SKF-525A, a metabolic inhibitor, produced liver damage and a marked increase in THC induced lethality (77).

New data on the effects of marihuana and tobacco smoke on human lung explants (70, 71) confirmed previous findings from studies with mice conducted by the same laboratory that both marihuana and tobacco "evoke not only abnormalities in DNA synthesis, mitosis and growth of fibroblastic cells of human lung explants, but also result in alterations of DNA" (71). The finding that these changes are observed very early and persist for prolonged periods after exposure indicates that these alterations are not lethal to cells. While additional preclinical studies are being undertaken to determine whether inhaled marihuana smoke plays a role similar to tobacco smoke in pulmonary carcinogenesis, Leuchtenberger and his colleagues caution that no conclusions should be drawn until the results of epidemiological studies and chronic preclinical inhalation experiments with marihuana cigarettes are completed. Confirmation of a previous report that marihuana tar painted on mice produces metaplasia of the sebaceous glands which often correlates with carcinogenicity indicates the need for additional studies in this area (70). The improved techniques for administering marihuana smoke to animals from higher species should aid in the study of long-term toxic effects of marihuana smoking.

Preliminary findings regarding the effects of marihuana on reproduction and development have continued. Effects on the mother and the young are definitely related to dose, route of administration, and species used. The data are further confounded by differences between species, probably related to their differences in metabolism (i.e., the results in studies with rats usually were negative at behaviorally effective dose levels (52, 91, 124), while experiments with rabbits and mice indicate they may be more sensitive, especially at very high dose levels) (53, 76).

For limited acute toxicity studies of cannabinoids, a simple new biological method using as an indicator the process of regeneration in planarian worms has been developed (69). This method allows determination of the activity of very small amounts of cannabinoids and could be used with advantage in structure-activity-type or in neurochemical-type studies.

Pharmacological Effects

The previously reported anticonvulsive effects of cannabinoids have now been confirmed in different laboratories. Cannabinoids were found to be potent anticonvulsive agents in a variety of test procedures (e.g., against audiogenic seizures in rats (10, 18, 75) or seizures elicited by electrical stimulation, "kindling" of the limbic cortex and the amygdala) (28, 39), as well as against maximal electroshock (MES) or pentylenetetrazol (PTZ)-induced seizures (26). Although anticonvulsant potencies do not significantly differ, delta-8-THC is three times more neurotoxic than delta-9-THC, and both are without effect on minimal seizures and lethality induced by PTZ. However, tolerance is developed after repeated administration, and the antiepileptic property of cannabinoids disappears rapidly (39). The low protective indices (ratio between neurotoxic and effective dose) that have been found (26) suggest that delta-9- and delta-8-THC have poor therapeutic potential as antiepileptic drugs. Anticonvulsive effects of other components of marihuana were highlighted when Izquierdo et al. found that cannabidiol (CBD), like diphenylhydantoin, can produce decreases in hippocampal seizure discharges (61). Cannabidiol has little psychoactive activity in laboratory animals or man and may represent a separation effect (59).

New data have again shown that the electroencephalographic (EEG) effects of cannabinoids are highly variable and are related to species, dose, and duration of treatment. As researchers study the other marihuana cannabinoids, new central effects are being discovered. A power spectrum study of EEG changes in rabbits after i.v. infusion of 0.1-2.0 mg/kg delta-9-THC confirmed previous results which showed an increase in amplitude of low frequency components in the delta band and the appearance of either single or multiple spikes mainly in the motor and limbic cortices (41). These changes in EEG after administration of delta-9-THC are accompanied by autonomic effects (i.e., rapid fall in blood pressure and bradycardia) which are not seen with other hallucinogenic agents such as LSD-25, mescaline, and DOM. These compounds also evoke EEG desynchronization rather than synchronization, mostly localized in the lower brain stem. With delta-9-THC, the EEG synchronization is generalized with slowing more prominent in the cortical areas but also seen in subcortical areas. In the same species and at about the same dose levels, delta-9-THC failed to block the cortical desynchronization (arousal) produced by physostigmine, thus showing that central cholinergic sensitive neurons associated with EEG activation systems are *not* blocked by THC (25). In monkeys implanted with deep cortical electrodes, exposure to marihuana smoke induced distinct recording changes in the septal region, occasionally accompanied by changes in recordings from the cerebellum, thalamus, hippocampus, and orbital and temporal cortices (55). Curiously, delta-8-THC, when administered to cats i.p. or i.v., failed to produce any striking EEG and behavioral effects (129).

Effects of delta-9-THC on the sleep-wakefulness cycles of rabbits (42), cats (6), and man (5) have also been reported, with a decrease in REM sleep after acute administration.

Continuing the studies of the effects of delta-9-THC on the polysensory cortex, Boyd et al. (12) compared the effects of a number of psychoactive drugs such as LSD, mescaline, and phencyclidine on an evoked response sensitive to the effect of delta-9-THC. This group found that mescaline had effects very similar to those of delta-9-THC, thus increasing both early and late evoked responses and resembling those of stimulant drugs. These effects may be related to the changes in sensory perception produced by these compounds. A direct cortical site of action for changes in sensory perception was also emphasized by others (125). Delta-9-THC has been shown to exert a differential effect on lateral geniculate neurons in the rat, outlining the effect of this compound on the visual system (8). Units that fire when the eye is illuminated are inhibited by the compound, whereas those that discharge in the dark but are inhibited by light either remain unchanged or increase their rate of firing.

Acute administration of pharmacologically active cannabinoids delta-9-THC, delta-8-THC, and 11-OH-delta-9-THC also caused a highly significant but reversible reduction in nuclear membrane—attached ribosomes of infant rat brain cortical cells (55).

Studies on the tolerance to EEG changes have reported inconsistent results after long-term administration (95, 114).

The mechanism of action in THC and its metabolites was further defined in in vitro experiments. Delta-9-THC and/or its metabolite, 11-OH-delta-9-THC, were found to have an inhibitory effect on nerve conduction (13, 17, 106). In vitro, they surprisingly potentiate both the acetylcholine and adrenaline-induced contractions of isolated muscles (46). Changes in RNA and acetylcholine activity reported earlier in chronic experiments were found to be reversible after cessation of treatment (74).

The effect of delta-9-THC on the peripheral sympathetic nervous system was confirmed when it was reported that 20 mg/kg delta-9-THC injected subcutaneously for 7 days into rats produced a significant decrease in serum dopamine B-hydroxylase activity (88). This was also seen with ethanol, and these results are critically influenced by environmental setting. In naive animals, delta-9-THC appears to have a sympatholytic effect, whereas in animals subjected to immobilization stress delta-9-THC potentiates the sympathetic response (65, 88). Serotonin (5-HT) seems to be involved in the development of cannabis-elicited aggressive behavior after chronic treatment (87). After chronic treatment with cannabis extract, the 5-HT brain levels remained unchanged in the nonaggressive rats but were significantly decreased in the aggressive animals. Continuing their experiments with inhibition of the biosynthesis of prostaglandins by cannabinoids, Burstein et al. have shown that not only delta-9-THC but also other major cannabinoids like cannabinol and cannabidiol and the precursor olivetol possess the same inhibitory properties (15). This indicates that the inhibitory power of the cannabinoids resides in the aromatic portion of the molecule.

The neuroendocrine effects of cannabinoids are still unclear and seem to vary with route and duration of administration (22, 73, 98). Further experiments on their effects on pituitary growth hormone and gonadotropins are in progress.

Cardiovascular effects of cannabinoids have been further elucidated. Delta-9-THC has been shown to reduce the blood pressure of hypertensive rats. However, tolerance to this effect developed rapidly (8, 9, 83, 103). The hypotensive activity of delta-9-THC in anesthetized cats and dogs may be caused partially by an attenuation of cardiac output (20, 48). This may be mediated by direct and reflexogenic action on the cardiovascular centers in the brain (19). Apparently the hypotensive effect of delta-9-THC may be prevented by hypoxia, but its bradycardic effect is profound and independent of alterations in blood gas parameters (21).

The effects of tetrahydrocannabinol on body temperature have been reviewed by Haavik and Hardman (51) and are found in many species. They have been shown to be related to dose (32, 111), sex (11), route of administration (111), and duration of administration with tolerance developing in young animals (1). Interactive effects with barbiturates and various sedative hypnotic drugs (108, 112, 113), amphetamines (96), anesthetic agents (23), and chloramphenicol (2) have been reported, usually after acute administration. In one study attenuation of effects was seen after subchronic THC treatment (101), probably due to the development of tolerance.

In relation to the differential activities of delta-9-THC, cannabis extract and LSD, it was reported that cannabinoids—in contrast to LSD—increase the liver tyrosine—alpha-keto glutarate transaminase (TKT) and tryptophan pyrrolase (TPO) activities (99).

In the immunological area, several studies have produced data to show possible trends of immunogenicity. One study showed that rats could be immunized with a protein conjugate of THC, against the effects of THC as exhibited in a spontaneous motor activity test (115). This is presumably caused by the binding of delta-9-THC to anti-THC antibodies, thus preventing the delta-9-THC from reaching drug-receptor sites. Another paper presents "evidence for the possible immunogenicity of Delta-9-THC in rodents" (84). The percentage of blast transformation in cultured mice spleen cells observed after 3-H thymidine incorporation was increased by THC, which acts as other antigen substances. Nahas and colleagues hypothesize that "THC might constitute a hapten *in vivo* which could trigger an immune response, as indicated by blast transformation" (84) and may have implications for human health. More recent work (85) indicates that leukocytes from chronic marihuana users have a reduced responsiveness to stimulation by phytohemagglutinin as measured by thymidine uptake in cultured cells. This observation prompted studies on the rejection of skin grafts in mice (72). Delta-9-THC significantly prolonged the interval before grafts were rejected suggesting potential usefulness in transplants. This group also reported significant inhibition of solid tumor growth in mice by delta-8- and delta-9-THC (54). It appears that the cannabinoids may be interferring with the incorporation of nucleic acids into DNA and that these solid tumor cells are more sensitive than cells from other tissues.

Additional reports on miscellaneous pharmacologic effects of cannabinoids have also been published since the last report (49, 63, 94, 117, 118).

References

1. Abel, E. L.; McMillan, D.E.; and Harris, L.S. Tolerance to the behavioral and hypothermic effects of 1-delta-9-tetrahydrocannabinol in neonatal chicks. *Experientia*, 28(10):1188-1189, 1972.
2. Adams, H.R., and Sofia, R.D. Interaction of chloramphenicol and delta-1-tetrahydrocannabinol in barbital-anesthetized mice. *Experientia*, 29:181-182, 1973.
3. Agurell, S., et al. Synthesis of tritium-labelled tetrahydrocannabinol and cannabidiol. *Acta Chemica Scandanavia*, 27:1090-1091, 1973.
4. Aldrich, M.R. The psychedelic underground: Hash oil and marihuana extracts. *Los Angeles Free Press*, 10(1):24, January 5, 1974.
5. Barratt, E., et al. The effects of the chronic use of marihuana on sleep and perceptual-motor performance in humans. *Current Research in Marihuana*. London: Academic Press, 1972, pp. 163-19[illegible].
6. Barratt, E.S., and Adams, P.M. Chronic marihuana usage and sleep-wakefulness cycles in cats. *Biological Psychiatry*, 6(3):207-214, 1973.
7. Bercht. Personal communication.
8. Bieger, D., et al. Differential effects produced by delta-1-tetrahydrocannabinol on lateral geniculate neurones. *Neuropharmacology*, 12:269-273, March 1973.
9. Birmingham, M.K. Reduction by delta-9-tetrahydrocannabinol in the blood pressure of hypertensive rats bearing regenerated adrenal glands. *British Journal of Pharmacology*, 48:169-171, May 1973.
10. Boggan, W.O.; Steele, R.A.; and Freedman, D.X. Delta-9-tetrahydrocannabinol effect on audiogenic seizure susceptibility. *Psychopharmacologia*, 29:101-106, March 1973.
11. Borgen, L.A.; Lott, G.C.; and Davis, W.M. Cannabis-induced hypothermia: A dose-effect comparison of crude marihuana extract and synthetic delta-9-tetrahydrocannabinol in male and female rats. *Research Communications in Chemical Pathology and Pharmacology*. 5(3):621-626, 1973.
12. Boyd, E.S.; Boyd, E.H.; and Brown, L.E. The effects of some drugs on an evoked response sensitive to tetrahydrocannabinols. Submitted to *Journal of Pharmacology and Experimental Therapeutics*.
13. Brady, R.O., and Carbone, E. Comparison of the effects of delta-9-tetrahydrocannabinol, 11-hydroxy-delta-9-tetrahydrocannabinol and ethanol on the electrophysiological activity of the giant axon of the squid. *Neuropharmacology*, 12:601-605, 1973.
14. Britofilho, D. Isolational cannabinol, cannabidiol and tetrahydrocannabinol from *Cannabis sativa L.* by thin layer chromatography. *Revista de Quimica Industrial* (Rio de Janeiro), 41:15-16, 1972.
15. Burstein, S.; Levin, E.; and Varanelli, C. Inhibition of biosynthesis by the naturally occurring cannabinoids. *Biochemical Pharmacology*, 22:1-6, 1973.
16. Burnstein, S., et al. The urinary metabolites of delta-1-THC. In: *Cannabis and Its Derivatives*, edited by Paton, W.D.M., and Crown, J., London: Oxford University Press, 1972.
17. Byck, R., and Ritchie, J.M. Delta-9-tetrahydrocannabinol: Effects on mammalian nonmyelinated nerve fibers. *Science*, 108:84-85, 1973.
18. Carlini, E.A., et al. Cannabidiol and *Cannabis sativa* extract protect mice and rats against convulsive agents. *Journal of Pharmacy and Pharmacology*, 25:664-665, 1973.
19. Cavero, I., et al. Studies of the hypotensive activity of (-)-delta-9-trans-tetrahydrocannabinol on anesthetized dogs. *Research Communications in Chemical Pathology and Pharmacology*, 6(2):527-539, September 1973.
20. Cavero, I., et al. Effects of (-)-delta-9-trans-tetrahydro-

cannabinol on regional blood flow in anesthetized dogs. *European Journal of Pharmacology*, 20:373-376, 1972.

21. Cavero, I., et al. Certain observations on the interrelationships between respiratory and cardiovascular effects of (-)-delta-9-trans-tetrahydrocannabinol. *Research Communications in Chemical Pathology and Pharmacology*, 3(2):483-492 1972.
22. Chakravarty, I., and Ghosh, J.J. Cannabis and the oestrous cycles of adult rats. *United Nations Report*, ST/SOA/Ser. S/38 February 14, 1973.
23. Chesher, G.B.; Jackson, D.M.; and Starmer, G.A. Interaction of cannabis and general anesthetic agents in mice. Personal communication.
24. Cohn, R.A.; Barratt, E.S.; and Pirch, J.H. Marijuana responses in rats: Influence of castration or testosterone. *Proceedings of the Society of Experimental Biology and Medicine*, 146:109-113, 1974.
25. Consroe, P.F. Effect of delta-9-tetrahydrocannabinol on a cholinergic-induced activation of the electroencephalogram in the rabbit. *Research Communications in Chemical Pathology and Pharmacology*, 5(3):705-712, May 1973.
26. Consroe, P.F., and Man, D.P. Effects of delta-8-and delta-9-tetrahydrocannabinol on experimentally induced seizures. *Life Sciences*, 13:429-439, September 1973.
27. Contract Report HSM-42-71-79, *Toxicological Manifestations in Fisher Rats Treated Orally with Delta-9-Tetrahydrocannabinol at Doses Equivalent to American Marihuana and Hashish for 180 Consecutive Days*. Report of March 9, 1973.
28. Corcoran, M.E., et al. Acute antiepileptic effects of delta-9-tetrahydrocannabinol in rats with kindled seizures. *Experimental Neurology*, 40(2):471-483, 1973.
29. Dewey, W.L., et al. Distribution of radioactivity in brains of tolerant and intolerant pigeons treated with 3-H-delta-9-tetrahydrocannabinol. *Biochemical Pharmacology*, 22(3): 399-405, 1973.
30. DeZeeuw, R.A.; Wijsbeck, J.; and Malingre, T.M. Interference of alkanes in the gas chromatographic analysis of cannabis products. *Journal of Pharmacy and Pharmacology* 25:21-26, 1973.
31. Dingell, J.V. The intracellular localization of delta-9-tetra-hydrocannabinol in liver and its effects on drug metabolism *in vitro*. *Biochemical Pharmacology*, 22:949-958, 1973.
32. Englert, L.F.; Ho, B.T.; and Taylor, D. The effects of (-)-delta-9-tetrahydrocannabinol on reserpine-induced hypothermia in rats. *British Journal of Pharmacology*, 49: 243-252, 1973.
33. Eskes, D.; Verway, A.M.; and Witte, A.H. Thin layer and gas chromatographic analysis of hashish samples containing opium. *Bulletin on Narcotics*, 25:41-47, 1973.
34. Ehrlich, D. Liquid hashish is uncovered. *The Journal* (Addiction Research Foundation, Toronto, Canada), 31(1):11, January 1, 1974.
35. Fairbairn, J.W. and Liebmann, J.A. The extraction and estimation of the cannabinoids in *Cannabis sativa L.* and its products. *Journal of Pharmacy and Pharmacology*, 25:150-155, 1973.
36. Fenimore, D. Personal communication, 1973.
37. Fenselau, G., and Hermann, G. Identification of phytosterols in red oil extract of cannabis. *Journal of Forensic Science*, 17:309-312, 1972
38. Fentiman, A.F. *Analytical Techniques for Determination of Cannabinoids*. Contract Report HSM-42-72-183, October 8, 1973.
39. Fried, P.A., and McIntyre, D.C. Electrical and behavioral attenuation of the anti-convulsant properties of delta-9-THC following chronic administration, *Psychopharmacologia* (Berlin), 31(3):215-227, 1973.
40. Friedrich-Fiechtl, J., et al. Zu Nachweis and identifizerung von tetrahydrocannabinol in biologischen flussigkeiten. *Naturwissenschaften*, 60:207-208, 1973.
41. Fujimori, M.; Trusty, D.M.; and Himwich, H.E. Delta-9-tetrahydrocannabinol: Electroencephalographic changes and autonomic responses in the rabbit. *Life Sciences*, 12(1):553-563, 1973.
42. Fujimori, M., and Himwich, H.E. Delta-9-tetrahydrocannabinol and the sleep-wakefulness cycle in rabbits. *Physiology and Behavior*, 11:291-295, 1973.
43. Galanter, M., et al. Effects on humans of delta-9-tetrahydrocannabinol administered by smoking. *Science*, 176:934-936, 1972.
44. Garrett, E.R., and Hunt, C.A. Picogram analysis of tetrahydrocannabinol and application to biological fluids. *Journal of Pharmaceutical Sciences*, 62:1211-1214, 1973.
45. Garrett, E.R., in press.
46. Gascon, A., and Peres, A.L. Effect of delta-8- and delta-9-tetrahydrocannabinol on the peripheral autonomic nervous system *in vitro*. *Canadian Journal of Physiological Pharmacology*, 51:12-21, 1973.
47. Gill, E.W.; Jones, G.; and Lawrence, D.K. Contribution of the metabolite 7-hydroxy-delta-1-tetrahydrocannabinol towards the pharmacological activity of delta-1-tetrahydrocannabinol in mice. *Biochemical Pharmacology*, 22:175-184, 1973.
48. Graham, J.D., and Li, D.M. Cardiovascular and respiratory effects of cannabis in cat and rat. *British Journal of Pharmacology*, 49:[illegible]-10, 1973.
49. Green, K., and Pederson, J.E. Effect of delta-1-tetrahydrocannabinol on aqueous dynamics and ciliary body permeability in the rabbit. *Experimental Eye Research*, 15:499-507, 1973.
50. Gross, S.J. Personal communication, 1973.
51. Haavik, C.O., and Hardman, H.F. The effect of tetrahydrocannabinols on body temperature. *The Pharmacology of Thermoregulation*, Karger, Basel, 1973, pp. 400-416.
52. Haley, L., et al. The effect of natural and synthetic delta-9-tetrahydrocannabinol on fetal development. *Toxicology and Applied Pharmacology*, 21:450, 1973.
53. Harbison, R.D., and Mantilla-Plata, B. Prenatal toxicity, maternal distribution and placental transfer of THC. *The Journal of Pharmacology and Experimental Therapeutics*, 180(2):446-453, 1972.
54. Harris, L.S., et al. Retardation of tumor growth by delta-9-tetrahydrocannabinol. *Pharmacologist*, 16(2):259, 1974.
55. Hattori, T.; Jakubovic, A.; and McGeer, P.L. The effect of cannabinoids on the number of nuclear membrane-attached ribosomes in infant rat brain. *Neuropharmacology*, 12:995-999, 1973.
56. Heath, R.C. Marihuana: Effects on deep and surface electroencephalograms of rhesus monkeys. *Neuropharmacology*, 12:1-14, 1973.
57. Ho, B.T., et al. Delta-9-tetrahydrocannabinol and its metabolites in monkey brain. *Journal of Pharmacy and Pharmacology*, 24:414-416, 1972.
58. Hoffman, N.E., and Yang, R.K. Gas chromatography of delta-1-tetrahydrocannabinol. *Analytical Letters*, 5:7-11, 1972.
59. Izquierdo, I. Effect of anticonvulsant drugs on the number of afferent stimuli needed to cause a hippocampal seizure discharge. *Pharmacology*, 11:146-150, 1974.
60. Izquierdo, I., and Nasello, A. G. Effects of cannabidiol and of diphenylhydantoin on the hippocampus and learning. *Psychopharmacologia*, 31:167-175, 1973.
61. Izquierdo, I.; Orsingher, O.A.; and Berardi, A.C. Effect of cannabidiol and of other *Cannabis sativa* compounds on hippocampal seizures. *Psychopharmacologia*, 28:[illegible]-102, 1973.
62. Just, W.W.; Werner, G.; and Wiechmann, M. Determination of delta-1-tetrahydrocannabinol and its delta-1(6)-isomer in blood, urine and saliva of hashish smokers. *Naturwissenschaften*, 59:222, 1972.
63. Kosersky, D.S., et al. Antipyretic analgesic and anti-inflammatory effects of delta-9-tetrahydrocannabinol in the rat. *European Journal of Pharmacology*, 24:1-7, 1973.
64. Kuppers, F.J., et al. Cannabis-VIV: Pyrolysis of cannabidiol, structure elucidation of the main pyrolytic product. *Tetrahedron*, 29:2797-2802, 1973.

65. Lamprecht, F., et al. Effect of delta-9-tetrahydrocannabinol on immobilization-induced changes in rat adrenal medullary enzymes. *European Journal of Pharmacology*, 21:249-251, 1973.

66. Lemberger, L. Tetrahydrocannabinol metabolism in man. *Drug Metabolism and Disposition*, 1:461-468, 1973.

67. Lemberger, L., et al. Comparative pharmacology of delta-9-tetrahydrocannabinol and its metabolite, 11-hydroxy-delta-9-tetrahydrocannabinol. *Journal of Clinical Investigation*, 52:2411-2417, 1973.

68. Lemberger, L., et al. The *in vitro* and *in vivo* metabolism of delta-6a, 10a-dimethylheptyl-tetrahydrocannabinol (DMHP). *Journal of Pharmacology and Experimental Therapeutics*, 187, 1973.

69. Lenicque, P.M.; Paris, M.R.; and Poulot, M. Effects of some components of *Cannabis sativa* on the regenerating planarian worm dugesia tigrina. *Experientia*, 28:1399-1400, 1972.

70. Leuchtenberger, C.; Leuchtenberger, R.; and Schneider, A. Effects of marihuana and tobacco smoke on human lung physiology. *Nature*, 241:137-139, January 12, 1973.

71. Leuchtenberger, C.; Leuchtenberger, R.; and Ritter, U. Effects of marihuana and tobacco smoke on DNA and chromosomal complement in human lung explants. *Nature*, 242:403-404, 1973.

72. Levy, J.A., et al. Effects of delta-8- and delta-9-tetrahydrocannabinol on the immune responses in mice. *Pharmacologist*, 16(2):259, Fall 1974.

73. Ling, G.M., et al. Effects of chronically administered 1-tetrahydrocannabinol of adrenal and gonadal activity of male rats. *International Journal of Clinical Pharmacology*, 7(1): 1-5, 1973.

74. Luthra. Y.K.; Rosenkrantz, H.; and Braude, M.C. Differential neurochemistry and temporal pattern in rats treated orally with delta-9-tetrahydrocannabinol for six months. Submitted for publication.

75. Man, D.P., and Consroe, J.F. Anticonvulsant effect on delta-9-tetrahydrocannabinol sound-induced seizures in audiogenic rats. *IRCS International Research System*, March 1973.

76. Mantilla-Plata, B.; Clewe, G.L.; and Harbison, R.D. Teratogenic and mutagenetic studies of delta-9-tetrahydrocannabinol in mice. Abstract No. 2995, *Federation Proceedings*, 32(3):746, 1973.

77. Mantilla-Plata, B., and Harbison, R.D. Effects of phenobarbital and SKF 525A pretreatment, sex, liver injury and vehicle on delta-9-tetrahydrocannabinol toxicity. *Toxicology and Applied Pharmacology*, in press.

78. Masoud, A.N., and Doorenbos, N.J. Mississippi-grown *Cannabis sativa L.* III. cannabinoid and cannabinoid acid content. *Journal of Pharmaceutical Sciences*, 62:316-318, 1973.

79. Massam, A. Increase in illicit hash oil has British police concerned. *The Journal*. (Addition Research Foundation). 3(4):10, April 1, 1974.

80. McMillan, D.E., et al. Blood levels of 3H-delta-9-tetrahydrocannabinol and its metabolites in tolerant and non-tolerant pigeons. *Biochemical Pharmacology*, 22:383-397, 1973.

81. Mechoulam, R.; Brown, P.; and Gaoni, Y. Synthesis of delta-1-tetrahydrocannabinol and related cannabinoids. *Journal of the American Chemical Society*, 94:6159-6165, 1972.

82. Mechoulam, R., et al. Synthesis and biological activity of five tetrahydrocannabinol metabolites. *Journal of the American Chemical Society*, 94:7930-7931, 1972.

83. Nahas, G.G., et al. Tolerance of delta-9-tetrahydrocannabinol in the spontaneously hypertensive rat. *Proceedings of the Society of Experimental Biology and Medicine*, 142:58-60, January 1973.

84. Nahas, G.G., et al. Evidence for the possible immunogenicity of delta-9-tetrahydrocannabinol (THC) in rodents. *Nature*, 243:407-408, June 15, 1973.

85. Nahas, G.G., et al. Inhibition of cellular mediated immunity in marihuana smokers. *Science*, 183:419-420, February 1, 1974.

86. National Institute on Drug Abuse, Symposium: "Analysis of Cannabinoids in Body Fluids." Rockville, Maryland, December 6, 1973.

87. Ng, L.K., et al. Delta-9-tetrahydrocannabinol and ethanol: Differential effects on sympathetic activity in differing environmental setting. *Science*, 180:1368-1369, June 29, 1973.

88. Nilsson, I.M., et al. Metabolism of 7-hydroxy-delta-1(6)-tetrahydrocannabinol in the rabbit. *Acta Pharmaceutica Suecia*, 19:97-106, 1973.

89. Olsen, J.L., et al. Preparation of delta-9-THC for intravenous injection. *Journal of Pharmacy and Pharmacology*, 25:344, 1973.

90. Pace, H.B.; Davis, W.M.; and Borgen, L.A. Teratogenesis and marihuana. *Annals of the New York Academy of Sciences*, 191:123-131, 1971.

91. Palermo, J. III, and Carvalho, F.V. The effects of chronic cannabis treatment on the aggressive behavior and the brain 5-hydroxy-tryptamine levels of rats with different temperaments. *Psychopharmacologia*, 32:383-392, 1973.

92. Paris, M., et al. L'acide delta-1-tetrahydrocannabivarolique, nouveau constituant du *Cannabis sativa L. Comptes Ronde Academie Science* (Paris), 276:205-207, 1973.

93. Paris, M.R., and Paris, R.R. Importance de la chromatographie pour l'etude des constituants du *Cannabis sativa L. Bulletin de la Society Chemique de France*, 1:118-122, 1973.

94. Parker, J.M., and Dubas, T.C. Automatic determination of the pain threshold to electroshock and the effects of delta-9-THC. *International Journal of Clinical Pharmacology*, 7:75-81, 1973.

95. Pirch, J.H., et al. Studies on EEG tolerance to marihuana in the rat. *Archives of International Pharmacodynamics*, 203:213-220, 1973.

96. Pirch, J.H., et al. Antagonism of amphetamine locomotor stimulation in rats by single doses of marihuana extract administered orally. *Neuropharmacology*, 12:485-493, 1973.

97. Pitt, C.G., et al. Synthesis of 11-hydroxy-delta-9-tetrahydrocannabinol and other physiologically active metabolites of delta-8-and delta-9-tetrahydrocannabinol. *Journal of the American Chemical Society*, 94:8578-8579, 1972.

98. Poddar, M.K., and Ghosh, J.J. Effects of cannabis extract and delta-9-tetrahydrocannabinol on adrenocortical activity. *United Nations Report* ST/SOA SER S/36, November 10, 1972.

99. Poddar, M.K., and Ghosh, J.J. Effect of cannabis extract, delta-9-tetrahydrocannabinol and lysergic acid diethylamide on rat liver enzymes. *Biochemical Pharmacology*, 21:3301-3303, 1973.

100. Rasmussen, K.E.; Rasmussen, S.; and Svendsen, A.B. Gas-liquid chromatography of cannabinoids in micro quantities of cannabis by solid injection. *Journal of Chromatography*, 69:381-384, 1972.

101. Rating, D., et al. Effect of subchronic treatment with (-)-delta-8-transtetrahydrocannabinol (delta-8-THC) on food intake, body temperature, hexobarbital sleeping time and hexobarbital elimination in rodents. *Psychopharmacologia*, 27:349-357, 1972.

102. Razdan, R.K.; Uliss, D.B.; and Dalzell, H.C. Hashish, synthesis of 7-hydroxy-delta-1-tetrahydrocannabinol (THC): An important active metabolite of delta-1-THC in man. *Journal of the American Chemical Society*, 95:2361-2362, 1973.

103. Reiss, J. Thin-layer chromatographic separation of the constituents of hashish on pre-coated silica gel sheet. *Archives Toxikologia*, 29:265-266, 1972.

104. Rosenkrantz, T.; Heyman, I.A.; and Braude, M.C. Inhalation, parenteral and oral LD_{50} doses of delta-9-tetrahydrocannabinol in Fisher rats. *Toxicology and Applied Pharmacology*, in press.

105. Schneider, R.X. Personal communication, 1973.

106. Seeman, P.; Chau Wong, M.; and Moyyen, S. The mem-

brane binding of morphine, diphenylhydantoin and tetrahydrocannabinol. *Canadian Journal of Physiology and Pharmacology,* 50:1193-1200, 1973.

107. Segelman, A.B., et al. *Cannabis sativa L.* (marijuana) III. The RIM test: A reliable and useful procedure for the detection and identification of marijuana utilizing combined microscopy and thin-layer chromatography. *The Journal of Chromatography,* 82:151-157, 1973.

108. Sengstake, C.B. Interactive effects of marihuana and Na pentobarbital on heart rate in the rat. Submitted to *Science.*

109. Shani, A., and Mechoulam, R. New types of cannabinoid: Synthesis of cannabielsoic acid A by a novel photochemical cyclization. *Journal of the Chemical Society,* 5:273-274, 1970.

110. Shoyama, Y., et al. Cannabis IV: Cannabicyclolic acid. *Chemistry and Pharmacy Bulletin,* 20:1927-1930, 1972.

111. Sofia, R.D. Paradoxical effect for delta-1-tetrahydrocannabinol on rectal temperature in rats. *Research Communications in Chemical Pathology and Pharmacology,* 4(2):281-288, 1972.

112. Sofia, R.D., and Knobloch, L.D. The interaction of delta-9-tetrahydrocannabinol pretreatment with various sedative-hypnotic drugs. *Psychopharmacologia,* 30:185-194, 1973.

113. Sofia, R.D.; Kubena, R.K.; and Barry, H. III. Inactivity of delta-9-tetrahydrocannabinol in antidepressant screening tests. *Psychopharmacologia,* 31:121-130, 1973.

114. Stadnicki, S.W.; Schaeppi, U.; and Rosenkrantz, H. Delta-9-tetrahydrocannabinol: Subcortical spike bursts and motor manifestations in a Fisher rat treated orally for 109 days. Submitted to *Life Sciences.*

115. Strahilevitz, M., et al. Blocking of the effect of delta-1-tetrahydrocannabinol on spontaneous motor activity in the rat by immunization with a protein conjugate of delta-1-THC. *Life Sciences,* 14(10):1975-1989, 1974.

116. Stromberg, L. Minor components of cannabis resin II: Separation by gas chromatography, mass spectra and molecular weights of some components with shorter retention times than cannabinol. *Journal of Chromatography,* 68:248-252, 1972.

117. Thompson, G.R., et al. Comparison of acute oral toxicity of cannabinoids in rats, dogs and monkeys. *Toxicology and Applied Pharmacology,* 25(3):363-372, July 1973.

118. Thompson, G.R., et al. Chronic oral toxicity of cannabinoids in rats. *Toxicology and Applied Pharmacology,* 25(3):373-390, July 1973.

119. Turk, R.F.; Dewey, W.L.; and Harris, L.S. Excretion of trans-delta-9-tetrahydrocannabinol and its metabolites in intact and bile duct cannulated rats. *Journal of Pharmaceutical Sciences,* 62(5):737-740, May 1973.

120. Turner, C.T. *Shipment, Analysis and Storage of Marihuana.* Contract Report HSM-42-70-109, June 30, 1973.

121. Turner, C.T. Personal communication, 1974.

122. Turner, C.E., and Hadley, K.W. Constituents of *Cannabis sativa L.* III: Clear and discrete separation of cannabinol and cannabichromene. *Journal of Pharmaceutical Sciences,* 62:1083-1086, 1973.

123. Turner, C.E., and Hadley, K.W. Constituents of *Cannabis sativa L.* VII: Distinct separation of cannabinol and cannabichromene by gas chromatography and its application to the phenotype classification of cannabis. *Journal of Pharmaceutical Sciences,* in press.

124. Uyeno, E.T. Delta-9-tetrahydrocannabinol administration during pregnancy in the rat. *Proceedings of the Western Pharmacological Society,* 16:64-67, 1973.

125. Vasquez, A.J., and Sabelli, H.C. Electrophysiological studies with delta-9-tetrahydrocannabinol. *Drug Addiction: Behavioral Aspects,* New York: Futura Press, forthcoming.

126. Vree, T.B., et al. Identification of cannabicyclol with a pentyl or propyl side-chain by means of combined gas chromatography-mass spectrometry. *Journal of Chromatography,* 74:124-127, 1972.

127. Wall, M. E. *Synthesis of Radiolabeled Cannabinoids and Metabolites.* Contract Report HSM-42-71-108, October 25, 1973.

128. Wall, M.E., et al. Identification of delta-9-tetrahydrocannabinol and metabolites in man. *Journal of the American Chemical Society,* 94:8579-8591, 1972.

129. Wallach, M.B., and Gershon, S. The effects of delta-8-tetrahydrocannabinol on the electroencephalogram, reticular formation multiple unit activity and sleep in the cat, in press.

3 Preclinical Behavioral Effects

The three previous *Marihuana and Health* Reports have described in detail the advantages and methodologies of a preclinical behavioral analysis of cannabis. Accordingly, this section will concentrate on reviewing that literature pertaining to the effects of cannabinoids on animal behavior which has appeared since the last report. Recent literature pertaining to this subject has been voluminous and has involved a wide variety of animal subjects and experimental techniques. For the sake of exposition, the review has been organized around the following areas of study: unlearned behavior—activity, exploration, and motor tasks; consummatory behavior; aggressive behavior, dominance, and competition; avoidance learning and aversive control; reinforcement schedules and maze learning; discrimination learning; tolerance.

Unlearned Behavior: Activity, Exploration, and Motor Tasks

A substantial portion of the earlier literature on the preclinical behavioral effects of cannabinoids described the gross behavioral changes produced by these drugs in several different animal species. This earlier literature has been discussed in previous *Marihuana and Health* Reports and in two recent reviews of the behavioral pharmacology of marihuana (80, 87). In general, the cannabinoids have been shown to produce a variety of gross behavioral effects in animals, including: the adoption of abnormal body postures, abnormal movements, ataxia, catalepsy, and hyperactivity and hypersensitivity to external stimuli. Although researchers continue to make gross behavioral observations of their animal subjects, more and more of the recent behavioral research on marihuana has come to involve learned as opposed to unlearned gross behaviors. However, several experiments dealing with spontaneous activity, open-field exploration, and unlearned motor tasks in animals were published during the past year. For the most part, these experiments were designed to investigate the interactions between cannabinoids and some other experimental variable on unlearned behavior.

Cannabinoids generally suppress the spontaneous motor activity and exploration of animals, although findings regarding these effects are limited, as always, by drug-route, time-effect, and dose-response considerations (24, 41). Drew and Miller (23) recently investigated the effects of prior habituation to the experimental apparatus upon the relationship between motor activity and delta-9-THC. Habituated and nonhabituated groups of rats were compared as to the effects of intraperitoneal (i.p.) injections of delta-9-THC (0.5, 1.5, and 6.0 mg/kg) on locomotion in an activity wheel. The nonhabituated rats were injected prior to their first exposure to the apparatus. A dose of 6.0 mg/kg significantly decreased running activity. The habituated rats were injected prior to their fourth exposure to the apparatus. Significant increases in spontaneous running were produced by doses of 1.5 and 6.0 mg/kg. These results are in accord with prior research and suggest that THC at higher doses may serve to block or retard the process of habituation.

In a somewhat similar vein, the effects of prior acclimation to the laboratory environment on the behavior of rats in the open field under delta-8-THC (5.0 mg/kg) and delta-9-THC (2.5 mg/kg) were studied (97). Nineteen daily i.p. injections were given to groups of rats having either 1 day or at least 130 days of acclimation to the laboratory. All rats in the drug groups vocalized to tactile stimuli, a finding in agreement with previous reports of a drug-induced hyperreactivity to stimuli (53). All rats under both drug and acclimation conditions showed a decrease in exploration of the environment as measured by rearing, grooming, latency to respond, and defecation. However, whereas ambulation was decreased by both drugs after long-term acclimation, ambulation was unaffected or increased in the short-term acclimation groups. In accordance with another recent study of exploratory behavior by Jarbe and Henriksson (60), only slight signs of tolerance to delta-

9-THC were observed. No signs of tolerance were observed for delta-8-THC.

The open-field arena has been used to study the interactions of another parameter with delta-9-THC on unlearned behavior. Borgen et al. (8) observed the behavioral development of rat offspring whose mothers had received subcutaneous injections of delta-9-THC during the 10th through 12th days of gestation. As compared to control subjects, the experimental rat pups exhibited significant hyperactivity in the open field at 9 days of age. Decrements in rearing and grooming occurred at 13 and 17 days of age. However, these effects on open-field exploration were attenuated by the age of weaning. Since cross-fostering control procedures failed to reduce any of the reported effects, Borgen et al. (8) concluded that delta-9-THC had a direct action on the developing fetus.

The interactions between age and sex variables and delta-9-THC on the performance of rats in unlearned motor tasks have also been recently investigated. In an earlier study using adult rats, Potvin and Fried (95) studied the effects of acute (5 or less) and chronic (25 or more) i.p. injections of 0.5 and 4.0 mg/kg delta-9-THC on the latency of unlearned motor tasks including rotating rod, balance beam, black-white choice, and swimming tasks. All measures of motor behavior were impaired by the 4.0 mg/kg dose in the acute condition. However, rats in the chronic condition developed tolerance to the drug-induced impairments in unlearned behavior. In a followup study, Barnes and Fried (6) gave 4.0 mg/kg i.p. injections of delta-9-THC to immature (30-day-old) and adult (90-day-old) groups of rats. Two months later, both groups of rats were again injected with 4.0 mg/kg delta-9-THC and tested on rotating rod and balance beam motor tasks. The rats who had first received THC when immature developed tolerance to the drug-induced impairments in unlearned motor behavior more rapidly than did the rats who were adults when first drugged. Thus, it appears that the age of the subject at the time of first exposure to delta-9-THC interacts with later development of tolerance to the drug.

A series of unlearned behavioral tasks was earlier used by Cohn et al. (14) to study the effects of oral doses of delta-9-THC (5.0, 10.0, 20.0, and 40.0 mg/kg) on male and female rats. Female rats were found to be more affected by the drug than were male rats. In a more recent investigation of sex differences in response to marihuana, this group orally administered 20.0 mg/kg of delta-9-THC to castrated male rats and to female rats pretreated with testosterone (15). The experimental rats were compared to drug control rats with respect to their performance on a battery of unlearned tasks. The drug responses of male rats were increased by castration and those of female rats were decreased by pretreatment with testosterone. The authors suggested that the observed sex differences in response to marihuana may be related to the liver metabolism of delta-9-THC (15). In this regard, Cohn et al. (15) found that enzyme induction with phenobarbital in female rats did not alter the behavioral response to delta-9-THC, while enzyme inhibition with SKF-525A in male rats increased the delta-9-THC effects on the unlearned behavioral tasks.

Consummatory Behavior

Research prior to 1973 demonstrated that cannabinoids (delta-8-THC, delta-9-THC, hashish resin, pyrahexyl) can produce reductions in food and water intake, with a consequent weight loss, in male rats. Several more recent articles have appeared which tend to confirm and extend various aspects of these previous findings (1, 61, 69, 98). Abel et al. (1) extended the finding of a delta-9-THC produced weight loss to baby chickens. Doses of delta-9-THC (1.0, 10.0, and 100.0 mg/kg, intramuscular (i.m.)) were administered to newly hatched male and female chickens for 24 days. A dose-dependent loss in body weight occurred between days 12 and 24. In another study different groups of female rats were used to demonstrate that neither delta-8-THC (5.0 mg/kg) nor delta-9-THC (2.5 mg/kg) when administered i.p. for 23 days reduced food intake; but both drugs significantly depressed water intake (98). Delta-8-THC also produced a decrease in body weight which was maintained throughout the drug regimen. Jarbe and Henriksson (61) studied the effects of i.p. injections of delta-8-THC and delta-9-THC (1.25, 2.5, 5.0, and 10.0 mg/kg) in rats deprived of water for 23 hours. Water intake was decreased in a dose-related manner by both drugs. Food intake was significantly decreased by the 5.0 mg/kg and 10.0 mg/kg doses of delta-8-THC.

The physiological mechanisms by which cannabinoids produce changes in consummatory behavior have not as yet been clearly delineated. However, two recent rat experiments tend to implicate involvement of the lateral hypothalamus. Kilbey et al. (69) found that delta-9-THC depresses water consumption induced by carbachol, a long-acting cholinergic agonist. Wagner et al. (105) found that low i.p. doses of delta-9-THC (0.25, 0.375, and 0.50 mg/kg) enhance reinforcement schedule-induced drinking in nondeprived rats. These results were attributed to the presumed action of delta-9-THC on a lateral hypothalamic mediated motor control system (105).

There have been several informal accounts, in addition to some experimental reports, that marihuana or hashish ingestion increases consummatory behavior in humans (e.g., 56). It is not clear why opposite effects are generally produced by marihuana on consummatory behavior in humans and animals. This discrepancy may be due simply to differences between the species; or as suggested by Elsmore and Fletcher (27), the discrepancy may be produced because animal subjects are usually given doses of delta-9-THC which are several times larger than the average human dose. A further possibility was investigated by Gluck and Ferraro (42) who argued that humans may be considered to have adapted to a long-term deprivation regimen, and thus, investigations of food and water intake effects of delta-9-THC should be carried out in deprived animals. In the previously described rat experiments, either deprived animals or animals only acutely deprived had been tested. The rats were placed on a regimen of 23-hour deprivation of either food or water for a period of 150 days. The rats were subsequently given an oral delta-9-THC dose of 1.0 mg/kg for 12 days. Both food and water consumption were significantly increased by the drug as assessed by intake measures recorded during the rats' 1-hour daily access to food and water.

Two studies have demonstrated that delta-9-THC can interfere with the copulatory behavior of the male rat. Merari et al. (84) injected male rats i.p. with either 2.0 or 3.0 mg/kg of delta-9-THC can interfere with the copulatory behavior the latency to mount receptive females, ejaculate, and mount again. No significant changes were found in the number of intromissions or mounts. These results tend to suggest that the drug produces a decreased motivation to copulate. A marked reduction in successful intromissions was observed in male rats at higher doses by Corcoran et al. (18). These researchers gave i.p. injections of hashish resin (8.3 or 16.6 mg/kg of delta-9-THC) to male rats and obtained significant reductions in copulatory behavior. This reduction in sexual activity was not accompanied by an impairment of locomotor activity.

Grilly et al. (48) have provided some evidence that previous marihuana experience does not produce long-term aftereffects on reproductive activity. Chimpanzees with extensive prior histories of exposure to marihuana were mated either with each other or with drug-naive chimpanzees. No alterations of sexual activity were observed in the drug-experienced animals. The incidence of normal births where one or both parents had extensive prior marihuana experiences was the same as that for drug-naive control animals.

Aggressive Behavior, Dominance, and Competition

A variety of situations has been used to study the aggressive interactions between animals, usually rodents, under the influence of cannabinoids. Following the outline established in the third *Marihuana and Health* Report, the various aggression paradigms may be assigned to four categories: starvation-induced, shock-induced, isolation-induced, and predatory aggression. A generalization which emerges from the previous literature on aggression is that cannabinoids can inhibit or enhance aggressiveness in animals depending upon the behavioral situation and drug dose parameters used. However, with the exception of aggression induced by starvation or sleep deprivation (5), the majority of available evidence indicates that cannabinoids inhibit or block the appearance of aggressive responses.

Most of the aggression experiments published since the last report have involved predatory aggression. There were no experiments dealing exclusively with starvation-induced aggression and only one which investigated shock-induced aggression..

Shock-Induced Aggression

Dubinsky et al. (25) found that 3 hours following i.p. injections of mice with delta-9-THC (12.5, 25.0, and 50.0 mg/kg), fighting time between pairs induced by shock was reduced. Doses of delta-9-THC as low as 2.5 mg/kg likewise reduced shock-induced aggression in rats.

Isolation-Induced Aggression

The effects of delta-9-THC on aggression induced by isolation in mice were studied by Dubinsky et al. (25). Drug doses up to 20.0 mg/kg injected i.p. were effective in blocking aggressive behavior. In one other study of isolation-induced aggression, tenHam and vanNoordwijk (101) gave 30 daily i.p. administrations of delta-8-THC (50.0 mg/kg) or delta-9-THC (5.0 mg/kg) to isolated mice and Chinese hamsters. Both drugs initially suppressed aggressiveness. No tolerance to this suppressive effect was observed during the 30-day drug treatment period.

Predatory Aggression

With respect to predatory aggression, four recently published experiments confirm the fact that acutely administered delta-9-THC can block the muricidal activity of rodents (4, 20, 25, 70). Kilbey et al. (70) gave i.v. injections of delta-9-THC to rats (0.1, 0.25, 0.5, 1.0, and 2.5 mg/kg). Doses above 0.25 mg/kg significantly increased the rats' latency to attack and kill frogs, although none of the drug doses inhibited general motor activity. Thus, it would appear that the effects of delta-9-THC on frog-killing in rats is not due to an impairment of motor function. Dubinsky et al. (25) found that i.p. injections of delta-9-THC reduced muricidal activity in treated rats at a dose level below that which impaired unconditioned motor behavior. The ED_{50} for suppressing mouse-killing behavior in rats was determined to be 4.9 mg/kg. This dose level agrees well with the findings of D'Encarnaco (20) who found that 4.0 mg/kg, but not lower doses, of delta-9-THC injected i.p. blocked mouse-killing behavior in rats.

One additional study suggests that cannabinoids can have a dual action on muricidal behavior in rats. Alves and Carlini (4) gave 8.8 mg/kg i.p. injections of delta-9-THC to rats previously shown to be muricidal for four consecutive sessions. Mouse-killing behavior was blocked in these rats and no tolerance developed. However, when rats shown not to be muricidal were injected i.p. with the same dose for 40 days and put on a 22-hour food deprivation schedule, they developed mouse-killing behavior. Although these latter rats were tested for the effects of delta-9-THC when food was available, the possibility exists that the data obtained were influenced by the preceding food deprivation regimen (11). However, the authors suggest that suppression of muricidal activity may be due to the acute depressant effects of the drug. This may lead, in turn, to hyperemotionality or irritability—conditions which may be sufficient to induce muricide in nonkiller rats.

When pairs of rats engage in aggressive-fighting behaviors, one member of the pair usually establishes dominance while the other comes to exhibit defensive-submissive behaviors. Miczek and Barry (85) have shown that the effects of delta-9-THC on aggressive behavior depend, in part, on whether the drug is administered to the dominant or to the submissive member of a pair of fighting rats. Three i.p. doses of delta-9-THC (1.0, 2.0, and 4.0 mg/kg) were given either to dominant or to submissive rats. Administration of the drug to the dominant rat greatly reduced the dominance as indicated by a decrease in the number of attacks on the nondrugged, submissive rat. Administrations of the drug to the submissive rat led to an increase in the severity of injuries inflicted by the nondrugged, dominant rat. This occurred primarily as a result of a drug-induced impairment of defensive behaviors in the submissive rat—behaviors which serve to prevent or to minimize injury inflicted by dominant males in normal intraspecies fighting. Uyeno (103, 104) studied the effects of delta-9-THC on dominance in two experiments. Male rats were put into competition either for a food pellet (103) or for a female rat in estrus (104). In both experiments, an i.p. dose of 0.5 mg/kg of delta-9-THC maximally inhibited dominance behavior at 1.5 to 2.0 hours after injection. A dose-response determination conducted at the peak effect time further indicated that sexual dominance was decreased in drugged rats in a dose-related manner (0.25 to 1.0 mg/kg).

A water competition situation was used by Jones et al. (64) to study the effects of delta-9-THC on the social behavior of squirrel monkeys. Dominant, submissive, and both partners in a dyad of monkeys were administered oral doses of delta-9-THC (0.25, 0.5, and 1.0 mg/kg). Total competition was decreased, and noncompetitive social behavior was increased when both competitors received 1.0 mg/kg of delta-9-THC. However, competition increased when either the submissive member or both members of low competitive pairs received 0.25 mg/kg of the drug.

Avoidance Learning and Aversive Control

Research prior to 1973 did not establish the effects of delta-9-THC on the acquisition of a learned shock avoidance task. In some instances delta-9-THC had been found to retard avoidance learning while in others the drug had been shown to facilitate avoidance acquisition. Miller and

Drew (87) have suggested that these contradictory results may be attributed, in part, to the biphasic time-effect function of delta-9-THC. That drug dose parameters are important, as well, has been recently shown by Goldberg et al. (44). In this study, the acquisition of a shuttle box avoidance response was studied in mice. Low i.p. doses of delta-9-THC (1.25, 2.5, and 5.0 mg/kg) depressed acquisition of the avoidance response. High doses of the drug (10.0, 20.0, 40.0, and 80.0 mg/kg) facilitated acquisition of shuttle box avoidance.

Cannabidiol has also been shown to affect the acquisition of a shuttle box avoidance response in rats. Izquierdo and Nasello (58) gave i.p. cannabidiol injections (3.5 mg/kg) to one group of rats 20 minutes before a 60-trial acquisition period, and to a second group of rats after the 60th trial. Cannabidiol injected before the session reduced the number of avoidance responses during acquisition. Retention was assessed by testing both groups of rats 7 days later. No drug effects on retention were observed.

In contrast to the data on acquisition of avoidance, delta-9-THC has reliably been found to disrupt performance of an established avoidance response. This has been most recently demonstrated by Houser (57), who found that an oral delta-9-THC dose of 12.0 mg/kg significantly reduced response rate and increased the number of shocks received by monkeys under a Sidman avoidance task, and by Newman et al. (90) who found that 20.0 mg/kg of delta-9-THC given i.p. disrupted shuttle box avoidance in rats. Additionally, Davis et al. (19) have shown that the dimethyl heptyl derivative (DMHP) disrupts continuous avoidance behavior in monkeys. Both of the delta-9-THC studies also demonstrated the development of tolerance to the disruptive effects of the drug on shock avoidance performance. Tolerance developed within a few days in the Houser (57) study but took on the average of 14 days to develop in the Newman et al. (90) study.

However, Manning (77) has shown that the development of delta-9-THC tolerance under an avoidance schedule is partially determined by the behavioral consequences produced by the drug administration. Rats were given an oral dose of 30.0 mg/kg for 10-45 days. When the effect of delta-9-THC was to increase the number of shocks received by the rats, tolerance developed within 6 days. However, if the delta-9-THC produced a decrease in the number of shocks delivered to the rat, no tolerance developed even after 45 days of exposure to the drug regimen. One further aspect of tolerance was studied by Newman et al. (90). These experimenters demonstrated the existence of a cross-tolerance between delta-9-THC and ethyl alcohol and a low dose of pentobarbital. No cross-tolerance with delta-9-THC was observed in the avoidance task for morphine, chlorpromazine, or a high dose of pentobarbital.

Delta-9-THC seems to have either no effect, or only a minimal effect, on the acquisition of a passive avoidance response in rats and mice (88, 92, 96). Both of the rat studies tested for retention of the passive avoidance response. Pandina and Musty (92) found that neither an i.v. dose of 0.75 mg/kg nor 3.0 mg/kg of delta-9-THC affected retention, regardless of whether the rats had been habituated to the apparatus prior to testing or not. Likewise, Miller et al. (88) did not observe any passive avoidance retention effects of i.p. injections of delta-9-THC (either 5.0 or 15.0 mg/kg). However, Miller et al. did observe a retention loss in an active avoidance retest if 5.0 mg/kg of delta-9-THC were administered prior to the retention test.

Inconsistent findings on the effects of cannabinoids have been obtained in other aversive control situations besides that of avoidance. For example, Gonzalez et al. (45) observed that a marihuana extract reduced the conditioned emotional response to a stimulus previously associated with an unavoidable electric shock, while Robichaud et al. (96) found that delta-9-THC increased the amount of conditioned suppression obtained. These and other conditioned emotional response experiments have investigated the effects of cannabinoids on suppression of appetitively motivated behavior in the presence of a stimulus associated with unavoidable shock. In an interesting variation of this procedure, Houser (57) investigated the effects of delta-9-THC on shock-avoidance behavior in the presence of a stimulus associated with unavoidable shock. Prior to drugging, avoidance responding was facilitated in the presence of the unavoidable shock stimulus. This facilitation of avoidance responding was significantly attenuated by oral delta-9-THC doses between 4.0 and 12.0 mg/kg delta-9-THC. It is interesting to note that no tolerance was observed to the delta-9-THC produced reduction in avoidance responding during the stimulus, nor was this reduction directly related to drug-induced decreases in general motor activity.

One interpretation which has been given to the findings that cannabinoids disrupt established avoidance and conditioned emotional response behavior is that cannabinoids reduce fear and anxiety (e.g., 45, 57). However, this interpretation needs to be tempered by the findings that cannabinoids can increase the resistance to extinction of an avoidance response (59) and can produce analgesia to electric shock stimulation (67, 93). In a study by Kaymakcalan et al. (67), pain thresholds were determined for electrical stimulation of the tooth of the dog. Administration of delta-9-THC (1.0 mg/kg, i.v.) markedly increased the pain thresholds. However, daily administrations of delta-9-THC produced a tolerance to this analgesic effect within 8 days.

The effects of delta-9-THC on behavior undergoing electric shock punishment have been investigated in only one recent study (79). In this experiment pigeons responding on a schedule of food reinforcement received varying i.m. doses of delta-9-THC (0.1 to 1.8 mg/kg) and delta-8-THC (0.3 to 3.0 mg/kg) either while undergoing electric shock punishment or in the absence of punishment. Both THC compounds suppressed overall rates of response by both punished and unpunished subjects, although delta-9-THC was slightly more potent than delta-8-THC.

Another aversive control paradigm which has been used to study delta-9-THC is the "bait-shyness" test. A recent experiment by Corcoran (16) has confirmed the previous finding of Elsmore and Fletcher (27) that tastes, paired with delta-9-THC administrations, become aversive. In the Corcoran (16) experiment, water-deprived rats learned in a single trial to avoid fluids whose taste was paired with i.p. injections of a potent hashish extract. Similar aversion conditioning was observed on subsequent pairings with other novel tastes in the same animals. Thus, the drug-induced bait-shyness was not solely a function of the novelty of the drugged state. Furthermore, it was found that if the rats were pretreated with an inhibitor of drug metabolizing hepatic enzymes, the strength of the hashish-induced aversion was greatly reduced. These latter results suggest that the noxious effects produced by hashish in this situation may be due to metabolites of delta-9-THC.

Reinforcement Schedules and Maze Learning

The effects of cannabinoids on appetitively reinforced learned behaviors have been studied in a wide variety of contexts, but most predominantly in the contexts of operant schedules of reinforcement and instrumental maze or alley learning. With respect to operant reinforcement schedules, two major types of experiments have been performed: (a) experiments in which the schedule itself is paramount, that is, where the interest is in cannabinoid-produced changes in the schedule-controlled behavior itself, and (b) experiments in which reinforcement schedule generated behavior is used simply as a baseline for the study of drug or other related behavioral parameters. Both types of experiments provide evidence regarding marihuana behavior interactions, but the focus differs between the two.

Previous marihuana research with reinforcement schedules was mostly of the first type of experiment and served well to delineate the effects of cannabinoids on schedule-controlled behavior. Generally, it was found that reinforcement schedule behavior is depressed in a dose-related manner by cannabinoids, although under differential and temporally related schedules, which are most likely to generate low response rates, a biphasic dose-response function was sometimes obtained. The details and nuances of the effects of cannabinoids on various reinforcement schedules have been described by McMillan (80) and in the previous *Marihuana and Health* Reports. Recently, there have been very few experiments designed explicitly to study the effects of delta-9-THC on reinforcement schedule controlled behavior (e.g., 19, 105). These studies tend to replicate and confirm the findings from previous research.

One advantage of the prior extensive research on reinforcement schedule controlled behavior and marihuana is that reinforcement schedules may now be considered as specified, reactive baselines for the further study of drug-related parameters. Indeed, reinforcement schedule baselines have been used to make between-drug comparisons, to compare routes of drug administration, and to study the long-term effects of delta-9-THC since the third report.

A variable interval schedule was used to compare the behavioral effects of delta-9-THC with those of 11-OH-delta-9-THC in pigeons (71). Identical i.v. doses of both compounds were given to different groups of pigeons (0.03, 0.10, and 0.30 mg/kg). With respect to dose and duration of action, delta-9-THC and 11-OH-delta-9-THC produced indistinguishable effects on the pigeons' responses to a variable interval schedule. Furthermore, development of tolerance to both compounds (0.30 mg/kg, i.v.) followed a similar course, and a reciprocal cross-tolerance was demonstrated between 11-OH-delta-9-THC and delta-9-THC. A fixed interval reinforcement schedule was used by Newman et al. (90) to study cross-tolerance between delta-9-THC and ethyl alcohol. Rats were first made tolerant to 20.0 mg/kg of delta-9-THC under the fixed interval schedule and then challenged with 1.0 and 3.2 g/kg ethyl alcohol. Cross-tolerance was observed to the low, but not to the high dose, of ethyl alcohol.

In another experiment, vehicle and route of administration were compared as factors influencing response rate on a fixed ratio schedule of reinforcement in rats. The results obtained indicate that delta-9-THC is absorbed well from aqueous solutions but poorly from oil solutions after i.p. injections. Absorption from a subcutaneous site of administration was delayed but still significant. Polyvinylpyrrolidone gave the most rapid absorption, while polysorbate 65 plus sorbitan monolaurate gave the most prolonged action on fixed ratio responding.

Route of delta-9-THC administration has been investigated in three additional studies, all of which used variable interval reinforcement schedule baselines. Abel et al. (2) administered from 0 to 10.0 mg/kg delta-9-THC either i.m., i.v., or p.o. (peroral) into pigeons. Onset of action was much faster for the i.v. route than for the other routes of administration. Both onset and duration of action were also directly related to drug dose. Additionally, a delta-9-THC tolerance developed at about the same rate with all three routes of administration. In two other studies (28, 30) orally administered delta-9-THC resulted in similar effects of drug dose on the rats' variable interval schedule responding (dose range from 0.25 to 64.0 mg/kg were used). Moreover, the oral dose-response curve obtained by Ferraro and Gluck (30) was comparable in form and dose magnitude to that obtained in a previous study by Grisham and Ferraro (50) in which rats responded on a variable interval schedule to i.p. injections.

Differential reinforcement of low rate schedules (DRL) was used to study both long-term and short-term behavioral effects of orally administered delta-9-THC in primates. Baseline DRL responding in chimpanzees over a period of 7 months (during which time the animals received a number of aperiodic doses of marihuana extract) was not affected by long lasting or cumulative drug effects (35). Manning (76) obtained characteristic dose-related effects of delta-9-THC (0.07-2.86 mg/kg, p.o.) on DRL responding in rhesus monkeys. However, a within-session analysis of the DRL behavior indicated that the drug-induced performance changes were less pronounced in the second half of the session. The nature of the within-session changes was investigated by comparing DRL performance at different postinjection times. The obtained data suggest that the improvement in DRL performance observed during the session was due to the monkey's responding under the influence of delta-9-THC rather than to the mere exposure of the animals to the drug.

An interesting application of reinforcement schedules was made by Cherek et al. (12, 13) to study the effects of delta-9-THC on food reinforced responding and aggression. Pigeons responded to one key on a fixed interval schedule for food reinforcement and to a second key on a fixed ratio schedule for the opportunity to attack a restrained target bird. The doses of delta-9-THC used (0.125 and 0.25 mg/kg) produced only minimal changes in the rate of fixed interval food reinforced responding but markedly suppressed the rate of responding for the opportunity to attack the target pigeon.

Despite the large number of experiments which have studied the effects of cannabinoids on reinforcement schedule controlled behavior, the effects of delta-9-THC on the acquisition and extinction of reinforcement schedule behavior have been investigated in only a single experiment. Ferraro et al. (32) gave i.p. injections (0.5, 2.0, and 8.0 mg/kg) to groups of rats throughout the course of variable interval reinforcement schedule acquisition training and subsequent extinction. A dose-dependent decrease in variable interval responding was obtained during both the acquisition and extinction phases of the research.

Relative to the amount of previous operant schedule work, the effects of cannabinoids on the acquisition and performance of instrumental maze responding have not been studied extensively. Moreover, prior research on maze learning has been somewhat contradictory, although the bulk of the evidence suggests that maze learning is impaired by delta-9-THC. Three recent rat experiments (24, 62, 102) provide additional evidence that a wide range of i.p. doses of delta-8-THC and delta-9-THC act to impair maze learning in a variety of experimental situations (Y maze, T maze, and Lashley III maze).

In one of these, rats were trained to traverse a Lashley III underwater maze (102). Rats were given i.p. injections of 4.0 mg/kg of delta-9-THC either 1.0, 1.5, 2.0, or 2.5 hours prior to swimming the maze. The peak effect of the drug was obtained after 2.0 hours. A second series of groups was injected with 1.0, 2.0, 4.0, and 8.0 mg/kg of delta-9-THC and made to swim the maze at the peak drug-effect time. A dose-related increase in maze errors occurred under the drug.

An experiment by Miller and Drew (86) demonstrated that delta-9-THC can also impair latent learning of a complex maze. Groups of rats were tested with vehicle or drug during initial exploration of a maze. All rats were then given maze acquisition training for food in the drug-free state. The rats initially given delta-9-THC did not evidence any facilitation effect from their preexposure to the maze (i.e., they did not exhibit the latent learning effect as did the rats initially given only the vehicle).

Marihuana impairs the acquisition of instrumental straight alley performance in rats (91) as well as nonspatial single alternation behavior. Miller et al. (89) trained rats to traverse a straight alley under conditions in which reward trials were alternated with nonreward trials. The rats learned to run faster on reward trials than on nonreward trials. Delta-9-THC at doses of 2.0, 3.0, and 5.0 mg/kg, i.p., disrupted the learned alternation behavior by decreasing running speed on reward trials and increasing running speed on nonreward trials. The obtained results suggest that delta-9-THC may disrupt reward expectancy or produce an inability to recall or to discriminate internal cues which predict whether the current trial is a reward or nonreward trial.

Discrimination Learning

The effects of cannabinoids on discrimination learning have not been extensively reviewed in previous *Marihuana and Health* Reports. There are two major subtopics relating cannabinoids and discrimination learning. The first involves the acquisition of stimulus control of behavior based on the presence or absence of cannabinoids. The second involves the effects of cannabinoids on the performance of discriminations based on exteroceptive stimuli.

Several experiments have earlier demonstrated that rats can learn to discriminate between the saline solution and cannabinoids (7, 9, 54, 72). More recent demonstrations that delta-9-THC can serve as a discriminative stimulus in the rat have been provided by four other studies (46, 55, 60, 63). In each of these latter studies, either a fixed dose of delta-9-THC (ranging from 1.0 mg/kg to 5.0 mg/kg, i.p.) or vehicle was administered at the same time prior to each experimental session. The rat was required to make a discriminative response based upon its current drug state. A similar procedure was used (33) to establish a delta-9-THC stimulus discrimination in rhesus monkeys. However, following the establishment of the drug-stimulus discrimination, Ferraro et al. (33) varied either the dose of delta-9-THC administered or the time of drug administration. Data obtained suggest that delta-9-THC may have both quantitative and qualitative stimulus properties which lie along continua associated with drug dose and time of drug administration.

Of recent concern has been the issue of whether or not tolerance develops to the drug-stimulus properties of delta-9-THC. The issue was opened by Bueno and Carlini (9) who demonstrated that rats could learn a bar-press discrimination based on the presence or absence of marihuana extract after the rats had been shown to develop tolerance to the drug under a rope-climbing task. Related to this are the findings that delta-9-THC discriminations remain stable over time and persist even when response rate depressant effects of the drug recover to control levels (33, 46). Two direct tests of tolerance to the stimulus effects of delta-9-THC have recently been made (55, 60). In the Jarbe and Henriksson study (60), the acquisition of a delta-9-THC discrimination (5.0 mg/kg, i.p., versus vehicle) was compared between drug-experienced and drug-naive rats. Although all rats learned the discrimination, the drug-naive rats did so with fewer errors. In the Hirschhorn and Rosencrans study (55), rats were first allowed to acquire the delta-9-THC discrimination (4.0 mg/kg, i.p., versus vehicle) and then were exposed to a 2-month chronic regimen of delta-9-THC administrations (8.0-32.0 mg/kg, i.p.) given after the experimental sessions. Although the rats in this latter experiment maintained the drug discrimination during the 2-month period, the degree of discrimination performance was somewhat reduced. Thus, it would seem that, at most, a slow and partial tolerance develops to the stimulus properties of delta-9-THC.

A phenomenon related to the stimulus properties of delta-9-THC is that of state-dependent learning. In essence, the phenomenon is that animals are more likely to perform better if trained and tested in the presence of a drug than if trained in a drug state and tested in the nondrug state, or vice versa. The earlier literature pertaining to delta-9-THC and state-dependent learning has been reviewed by Miller and Drew (87). Briefly, it has been shown that rats trained and tested on a behavioral task under delta-9-THC perform better than rats trained under delta-9-THC and tested in the nondrug state or trained in the nondrug state and tested under delta-9-THC (e.g., 62). A recent demonstration of delta-9-THC state-dependent learning in mice has been completed (44). In this latter study, mice trained under delta-9-THC and switched to the drug vehicle alone, or to chlordiazepoxide, performed worse than mice maintained in the delta-9-THC drug state.

Until recently, there have been only a few studies which have investigated the effects of delta-9-THC on the performance of discriminations based on exteroceptive stimuli. These studies have been reviewed recently by Ferraro et al. (31). In general, the effects of delta-9-THC on established stimulus discriminations are influenced by the same variables that determine the effects of other psychotropic drugs on discrimination performance. Thus, delta-9-THC is more likely to disrupt discrimination performance if the discriminative stimuli are presented successively than if they are presented simultaneously (31). Disruption of a successive stimulus discrimination by delta-9-THC is typically due to an increase in response to the stimulus associated with nonreinforcement and a dose-related decrease in response to the stimulus associated with reinforcement (39, 105). Excitatory or inhibitory generalization gradients, obtained following successive discrimination training, are not usually disrupted by delta-9-THC (72, 76). However, Lyons et al. (74) obtained a dose-related change in the generalization gradient after i.p. delta-9-THC doses of up to 2.0 mg/kg of delta-9-THC. Disruption of discrimination performance under delta-9-THC is more likely if the stimulus control contingencies are complex than if they are simple (3, 31, 43).

In this latter context, the acquisition and reversal of a two-choice color discrimination between monkeys which received an oral dose of 1.0 mg/kg delta-9-THC were compared to those which received the drug vehicle alone (43). Although acquisition of the initial simultaneous discrimination did not differ between the drug and control animals, subsequent discrimination reversals were markedly retarded by delta-9-THC. Furthermore, in a recent series of experiments by one group (34, 36, 37, 47, 49), delta-9-THC has been shown to consistently impair the performance of chimpanzees under delayed conditional discrimination tasks. However, these latter experiments may reflect drug-induced impairments in short-term memory more than they do decrements in discrimination performance per se. In one other conditional discrimination experiment, monkeys administered a wide range of oral doses (1.0-16.0 mg/kg) of delta-9-THC showed a dose-related decrement in performance along both temporal and auditory stimulus dimensions (26).

Although delta-9-THC typically impairs discrimination performance based on exteroceptive stimuli, it does not always affect visual perception. This was shown by Fried and Husband (40) who studied the effects of acutely and chronically administered delta-9-THC on depth perception in rats. No evidence that delta-9-THC (0.5 or 4.0 mg/kg, i.p.) affected depth perception was obtained in this experiment.

Tolerance

The literature discussed in the preceding sections attests that tolerance to delta-9-THC occurs in an array of situations and species, and under several behavioral and drug conditions. There seems to be little doubt that delta-9-THC tolerance development can be characterized by its rapid development, large magnitude, and wide generality, as has been stated in the third *Marihuana and Health* Report. A cursory sampling of the literature presented above shows that delta-9-THC tolerance develops for: unlearned motor responses in rats, analgesia in dogs, food reinforcement schedule performance in pigeons, and shock avoidance performance in primates. Additionally, delta-9-THC was shown to evidence cross-tolerance to other cannabinoids and to some sedative-hypnotic drugs.

On the basis of findings such as these, McMillan et al. (82) have suggested that tolerance to delta-9-THC is a pharmacodynamic tolerance based on cellular mechanisms. From more recent work by this group of researchers, it seems reasonable to conclude that delta-9-THC tolerance is not a metabolic or drug dispositional tolerance. When comparing the metabolic response of tolerant and nontolerant pigeons to an injection of delta-

9-THC, it was found that tolerant pigeons respond to delta-9-THC at the same rate and with the same pattern as nontolerant pigeons (83). The levels of delta-9-THC and its metabolites were as high in the blood of tolerant animals as they were in nontolerant animals. Dewey et al. (22) found that radiolabeled delta-9-THC produces similar levels of radioactivity in the brains of tolerant and nontolerant pigeons. Thus, tolerance to delta-9-THC does not seem to be due to distributional differences which produce a decreased concentration of total cannabinoids in the brain.

The recent literature reviewed in the preceding sections demonstrates, as well, that delta-9-THC tolerance does not develop in all situations, nor at the same rate for all behaviors in the same situation. Again, the literature above indicates that delta-9-THC tolerance does not develop, or is very slow to develop, for: open-field behavior in rats, isolation-induced aggression in mice; drug-stimulus discriminations in rats; and complex discriminations in primates. Additionally, tolerance was shown to develop at different rates for shock avoidance and food reinforcement schedules and for different response components of an avoidance learning situation. It is not possible to specify all of the reasons for the variability in delta-9-THC tolerance found in different experiments. The studies reviewed differ in nonsystematic ways with respect to behavioral tasks, species of subject, and drug-related parameters such as drug dose, number and distribution of drug administration, and route of drug administration. Consequently, direct comparisons between these experiments would not be valid.

Several researchers (e.g., 26, 38, 51) have suggested that learning or drug behavior interactions play a role in the development of tolerance to delta-9-THC as they have been shown to do in the development of tolerance to other psychotropic drugs. It is possible that learned and pharmacodynamic tolerance to delta-9-THC are simply manifestations of similar underlying mechanisms in accordance with a suggestion made by Kalant et al. (65). However, on the basis of the literature, it seems evident that learning mechanisms can account for some—although by no means all—characteristics of tolerance to delta-9-THC.

The role of behavioral adjustments to marihuana-produced effects on learned behavior has been emphasized by Ferraro (29). Briefly stated, this position suggests that behavioral tolerance to marihuana should occur only when the drug produces impairments in performance or alters the environment so as to be to the decrement of the organism. Even in these instances, tolerances should only occur if the organism can learn to make behavioral adjustments which serve to counteract the adverse behavioral effects produced by the drug. A number of studies were conducted during the past year which experimentally analyzed the behavioral factors that contribute to the development of tolerance to delta-9-THC.

In a previously described experiment (77), it was found that if delta-9-THC acted to increase the number of shocks received by rats under an avoidance schedule, then tolerance developed within 6 days. However, if the effects of the drug were to decrease shock rate, tolerance did not develop within up to 45 days.

In another previously described experiment by Manning (76), it was found that within-session tolerance to the effects of delta-9-THC on monkeys DRL responding were not the result of mere exposure to the drug, but rather were dependent upon the monkeys responding under the influence of the drug. These data are consistent with the hypothesis that organisms must learn behavioral adjustments to the effects of cannabinoids in order for tolerance to be manifested. Additional evidence that the opportunity to respond under the influence of delta-9-THC is an important factor in the development of tolerance was provided by Carder and Olson (10). Rats were trained to lever press for food or water reinforcement and given i.p. injections of marihuana extract (4.0 mg/kg, delta-9-THC), either prior to or after behavioral testing. Rats which responded under the influence of the drug developed tolerance, while those rats who had received delta-9-THC outside of the test situation did not. A related set of delta-9-THC findings was obtained in chimpanzees by Ferraro and Grilly (36).

The amount of prior training on a learning task has been shown to influence directly the magnitude of the behavioral effects produced by delta-9-THC (36) and the rate of tolerance developed to the drug (91). Olson and Carder (91) found that rats trained to run an alley under the influence of an oral dose of marihuana extract (6.0 mg/kg, delta-9-THC) showed a very slow improvement in performance during training. Those rats which received the marihuana extract after asymptotic performance had been achieved exhibited an initial disruption under the drug and then rapidly developed tolerance.

In contrast to the rapid delta-9-THC tolerance which typically develops in animals performing under simple behavioral tasks, a lack of tolerance has been reported in animals working under more complex behavioral tasks. Failure to observe tolerance in a study wherein monkeys worked on a complex schedule of reinforcement after oral administration of 2.0 mg/kg delta-9-THC was attributed to the complexity of the tasks (99). Further, it was implied that the difficulty of learning responses, which compensate for drug-produced impairments in performance, is an increasing function of the complexity of the baseline task used. A similar conclusion was reached by Ferraro and Grilly (34) who failed to observe tolerance to oral doses of delta-9-THC (1.0 and 4.0 mg/kg) in chimpanzees working long-delay matching-to-sample problems.

In one of a series of experiments on delayed matching-to-sample performance in chimpanzees, Ferraro et al. (37) determined that tolerance to delta-9-THC does occur under delayed matching-to-sample baselines, but only if the delay interval used is short. Similarly, Grilly et al. (49) found that chimpanzees administered oral doses (1.0 mg/kg) of delta-9-THC developed tolerance at specific delay values of a matching-to-sample task. However, this tolerance did not transfer when the delay interval was increased. These researchers argued that if compensatory responses are learned under delta-9-THC, then they should be specific to the particular stimulus situation used and should be relatively permanent. Thus, tolerance to delta-9-THC, once established in a specific stimulus situation, should be at least partially retained in that situation even after prolonged abstinence from the drug is enforced. This implication was investigated with chimpanzees who had already developed tolerance to delta-9-THC under a short-delay matching-to-sample problem (37). These chimpanzees were first exposed to a long-delay problem, where no tolerance was observed, and then given additional training in a drug-free state. Complete tolerance to delta-9-THC was observed when the chimpanzees were returned to the original short-delay problem and administered the same oral dose of delta-9-THC (0.75 or 1.0 mg/kg).

The literature pertaining to delta-9-THC tolerance suggests that both pharmacodynamic and behavioral factors are important determinants of the development of marihuana tolerance. To fully elucidate the characteristics of marihuana tolerance, continued research in this area will be necessary.

Recently, a number of researchers have addressed themselves to earlier reports that delta-9-THC may produce physical dependence and abstinence in monkeys (21, 66) and that monkeys will self-administer delta-9-THC (94). While the details of the experimental procedures vary among these recent experiments, the fundamental approach is the same. Animals are first given forced exposure to delta-9-THC and are then tested to determine whether they will self-administer the drug or prefer the drug over a nondrug substance.

In one of these studies, monkeys prepared with indwelling jugular catheters were used to determine whether monkeys would self-administer delta-9-THC (52). These workers used a number of different procedures to induce drug self-administration. Among the procedures used were the substitution of delta-9-THC after the monkeys had been trained to respond for cocaine, gradually transferring the animals from a cocaine-THC mixture to THC alone, and infusing the monkeys for 30 days with 2.0 mg/kg delta-9-THC. In no instance did the animals self-administer delta-9-THC or show signs of withdrawal at the termination of a forced drug regimen.

Leite and Carlini (73) performed four experiments with rats and concluded that rats do not self-administer a cannabis extract, nor do they show abstinence symptoms after prolonged ingestion of the drug. In the longest experiment, rats were forced to drink a cannabis extract for 126 days. At various points in the drug regimen, the rats were withdrawn from the drug for up to 96 hours and then were given a choice between the cannabis extract and a control solution. As in the other Leite and Carlini (73) experiments, the rats preferred the control solution and showed no behavioral symptoms of abstinence.

Two additional experiments demonstrated that rats and mice are reluctant to consume cannabinoid preparations. Rats forced to drink a hashish suspension for over 30 days rejected the drug when water was made available (17). Maker et al. (75) found mice reluctant to consume food pellets containing delta-9-THC (5.0 mg/kg) even after subsisting on the pellets for over 2 months.

In addition, two long-term behavioral experiments failed to yield evidence of residual effects following termination of delta-9-THC administrations. In one of these (36), chimpanzees were administered oral doses of 1.0 mg/kg for 5 consecutive months on a delayed matching-to-sample baseline. In the other (35), the chimpanzees working in the scheduled-controlled operant procedure were aperiodically administered doses of marihuana extract over a 7-month period.

On the other hand, two reports appearing this year suggest that dependence and abstinence symptoms may be produced by delta-9-THC. Two monkeys were treated orally for 50 days with 37.5 mg/kg delta-9-THC (100). Upon termination of the drug treatment, both monkeys showed increased aggressiveness and one exhibited "hallucinations." In another study, Hirschhorn and Rosencrans (55) treated rats for a 5-week period with i.p. doses of delta-9-THC ranging from 8.0 mg/kg to 32.0 mg/kg. The rats were administered naloxone HCL on the last day of treatment. The rats exhibited narcoticlike withdrawal symptoms including diarrhea, teeth chatter, "wet dog" shakes, salivation, and ptosis. Despite the evidence to the contrary, the possibility that marihuana may produce a physical dependence needs to be further pursued.

In summary, research published during the past year in the areas of unlearned behavior, consummatory behavior, avoidance learning, and reinforcement schedule learning serves to confirm previous findings that marihuana exerts a primarily suppressive effect on a variety of animal behaviors. Continued research in these areas will be necessary in order to establish the mechanisms of action for the cannabinoids. The literature reviewed also indicates that research on the interactions between cannabinoids and complex behavior, particularly complex discrimination behavior, has been sparse. Behavioral paradigms for the study of memory and cognitive functions in animals are available in the psychological literature. The paradigms should now be increasingly used in the study of cannabinoid action. Certainly, the large amount of previous marihuana research on simpler behaviors has established the groundwork for the study of more complex behavior.

The literature reviewed did not include any research on the interactions of cannabinoids with other psychotropic drugs. Given the increase in polydrug use among humans, preclinical animal research on drug interactions would seem to merit a high order of priority. As was noted above, several behavioral paradigms have now been established as sensitive, reactive baselines for the study of marihuana effects. These baselines would be useful, as well, for the study of marihuana interactions with other drugs.

It is now safe to conclude that marihuana suppresses aggressiveness, dominance, and competition among nonstressed animals. The research conducted since the last report shows, with occasional exception, that marihuana blocks aggression in experimental situations where, under nondrug conditions, killing and intense fighting behavior would be expected. These findings need to be pursued in studies of marihuana and human aggression. Models for testing human aggression are also available in the psychological literature (e.g., 68). Such models could be applied in studying the interactions between human aggression and marihuana smoking.

Although there are only occasional suggestive animal findings to the contrary, it might do well to hold in abeyance any strong conclusion that marihuana does not produce a drug dependence. The animal research completed this past year was marked by an increase in long-term studies of marihuana. Further research on the chronic effects of the drug may be anticipated in the course of next year and should provide more definitive evidence on the issue of drug dependence and the existence of marihuana-produced abstinence symptoms. Nevertheless, the existing literature clearly suggests that animals will voluntarily self-administer marihuana compounds only with reluctance, if at all. These findings conflict with the well-established, widespread ingestion of marihuana by humans. It is hoped that further research on the reinforcing properties of marihuana in animals may serve to elucidate some of the factors which lead to the initiation and/or continued use of marihuana by humans.

One hypothesis in this regard is that marihuana is not reinforcing in and of itself but, instead, produces secondary effects which indirectly reinforce humans. The experiments cited above, which state that marihuana can produce state-dependent learning and can serve as the basis for discrimination learning, contribute to the likelihood of such a hypothesis. The research establishes that marihuana ingestion produces stimuli which are discriminable. Consequently, these stimuli are available for conditioning to other events, including reinforcing ones. At the least, the possibility that marihuana smoking produces secondary reinforcing properties in humans should be given further study.

It was concluded above that the development of marihuana tolerance is influenced by both pharmacodynamic and learning factors. The cellular mechanisms underlying pharmacodynamic tolerance remain to be specified. And the compensatory responses to the deleterious effects of marihuana—which are presumed to be learned while responding under the influence of marihuana—still need to be empirically identified. In this latter context, if it is to be assumed that organisms learn compensatory responses when suitable, then it should be possible to demonstrate that they do so (and develop tolerance) in situations designed explicitly to provide for compensatory behavior. Alternatively, no tolerance should be observed in situations designed specifically to block the acquisition of learned compensatory behavior. Given that such demonstrations are successful, a behavioral analysis of tolerance could help to account for some of the inconsistencies reported in the literature concerning the development of marihuana tolerance in humans. For example, learning mechanisms might, in part, account for the differences in performance obtained between "marihuana-naive" and "marihuana-experienced" human smokers when they are tested under the influence of marihuana during demanding real-life simulation tasks.

By way of final summary, the animal literature reviewed in this section may be judged to highlight the importance of preclinical behavioral research in elucidating and interpreting the effects of marihuana. Furthermore, this research is useful in guiding the design of studies where humans are used as the experimental subjects.

References

1. Abel, E.L.; Cooper, C.W.; and Harris, L.S. Effects of delta-9-tetrahydrocannabinol on body weight and brain electrolytes in the chicken. *Psychopharmacologia*, 35:335-339, 1974.
2. Abel, E.L.; McMillan, D.E.; and Harris, L.S. Delta-9-tetrahydrocannabinol: Effects of route of administration on onset and duration of activity and tolerance development. *Psychopharmacologia*, 35:29-38, 1974.
3. Adams, P.M., and Barratt, E.S. The effects of a marijuana extract on two-choice discrimination learning in the squirrel monkey. Presented at the Psychonomic Society, St. Louis, 1972.
4. Alves, C.N., and Carlini, E.A. Effects of chronic and acute administration of *Cannabis sativa* extract on the mouse killing behavior of rats. *Life Sciences*, 13:75, 1973.
5. Alves, C.N.; Goyos, A.C.; and Carlini, E.A. Aggressiveness induced by marihuana and other psychotropic drugs in REM sleep deprived rats. *Pharmacology, Biochemistry and Behavior*, 1:183-189, 1973.
6. Barnes, C., and Fried, P.A. Tolerance to delta-9-THC in adult rats with differential delta-9-THC exposure when immature or during early adulthood. *Psychopharmacologia*, 34:181-190, 1974.
7. Barry, H. III, and Kubena, R.K. Discriminative stimulus characteristics of alcohol, marihuana, and atrophine. In: *Drug Addiction*, vol. 1, edited by Singh, J.M.; Miller, L.; and Lal, H., New York: Futura, 1972.
8. Borgen, L.A.; Davis, M.W.; and Pace, H.B. Effects of prenatal delta-9-tetrahydrocannabinol on the development of rat offspring. *Pharmacology, Biochemistry and Behavior*, 1:203-206, 1973.
9. Bueno, O.F.A., and Carlini, E.A. Dissociation of learning in marihuana tolerant rats. *Psychopharmacologia*, 25:49-56, 1972.
10. Carder, B., and Olson, J. Learned behavioral tolerance to marihuana in rats. *Pharmacology, Biochemistry and Behavior*, 1:73-76, 1973.
11. Carlini, E.A., and Masur, J. Development of aggressive behavior in rats by chronic administration of *Cannabis sativa* (marihuana). *Life Sciences*, 8:607-620, 1969.
12. Cherek, D.R., and Thompson, T. Effects of delta-1-tetrahydrocannabinol on schedule-induced aggression in pigeons. *Pharmacology, Biochemistry and Behavior*, 1:493-500, 1973.
13. Cherek, D.R.; Thompson, T.; and Heistad, G.T. Effects of delta-1-tetrahydrocannabinol and food deprivation level on responding maintained by the opportunity to attack. *Physiology and Behavior*, 9:795-800, 1972.
14. Cohn, R.A. et al. Sex differences in response to marihuana in the rat. *Drug Addiction: Experimental Pharmacology*, 1:227-234, 1972.
15. Cohn, R.A.; Barratt, E.S.; and Pirch, J.H. Marihuana responses in the rat: Influence of castration on testosterone. *Proceedings of the Society for Experimental Biology and Medicine*, 146:109-113, May 1974.
16. Corcoran, M.E. Role of drug novelty and metabolism in the aversive effects of hashish injections in rats. *Life Sciences*, 12:63-72, 1973.
17. Corcoran, M.E., and Amit, Z. Reluctance of rats to drink hashish suspensions: Free-choice and forced consumption, and the effects of hypothalamic stimulation. *Psychopharmacologia*, 35:129-147, 1974.
18. Corcoran, M.E., et al. Reduction in copulatory behavior in male rats following hashish injections. *Research Communications in Chemical Pathology and Pharmacology*, 1:779-982, 1974.
19. Davis, T.R.A.; Kensler, C.J.; and Dews, P.B. Comparison of behavioral effects of nicotine, d-amphetamine, caffeine and dimethyleptyl tetrahydrocannabinol in squirrel monkeys. *Psychopharmacologia*, 32:51-65, 1973.
20. D'Encarnaco, P.S. Neurocidal block produced by delta-9-tetrahydrocannabinol. Submitted for publication, 1974.
21. Deneau, G.A., and Kaymakcalan, S. Physiological and psychological dependence to synthetic delta-9-tetrahydrocannabinol (THC) in rhesus monkeys. *Pharmacologist*, 13: 246, 1971.
22. Dewey, W.L., et al. Distribution of radioactivity in brain of tolerant and nontolerant pigeons treated with ^{3}H-delta-9-tetrahydrocannabinol. *Biochemical Pharmacology*, 22:399-405, 1973.
23. Drew, W.G., and Miller, L.L. Differential effects of delta-9-THC on locomotor behavior in activity wheel habituated and nonhabituated rats. *Pharmacology*, 9:41-51, 1973.
24. Drew, W.G.; Miller, L.L.; and Baugh, E.L. Effects of delta-9-THC, LSD-25 and scopolamine on continuous spontaneous alternation in the Y-maze *Psychopharmacologia*, 32:171-182, 1973.
25. Dubinsky, B.; Robichaud, R.C.; and Goldberg, M.E. Effects of (-)-delta-9-trans-tetrahydrocannabinol and its selectivity

in several models of aggressive behavior. *Pharmacology,* 9:204-216, 1973.

26. Elsmore, T.F. Effects of delta-9-tetrahydrocannabinol on temporal and auditory discrimination performance of monkeys. *Psychopharmacologia,* 26:62-72, 1972.
27. Elsmore, T.F., and Fletcher, G.V. Delta-9-tetrahydrocannabinol: Aversive effects in rat at high doses. *Science,* 175:911-912, 1972.
28. Elsmore, T.F., and Manning, F.J. Time course and dose-response effects of orally administered delta-9-THC on interval schedule performance. Presented at Psychonomic Society, St. Louis, 1973.
29. Ferraro, D.P. Effects of delta-9-tetrahydrocannabinol on simple and complex learned behavior in animals. *In: Current Research in Marijuana,* edited by Lewis, M.F., New York: Academic Press, 1972.
30. Ferraro, D.P., and Gluck, J.P. Effects of oral delta-9-tetrahydrocannabinol on operant reinforcement schedule performance in rats. *Pharmacology,* 11:65-69, 1974.
31. Ferraro, D.P., et al. Interactions between drugs and the stimulus control of behavior. *In: Behavioral Models of Drug Dependence,* edited by Stretch, R., New York: Raven Press, in press.
32. Ferraro, D.P.; Gluck, J.P.; and Herndon, G.B. Acquisition and extinction of variable interval schedule behavior by rats under delta-9-tetrahydrocannabinol. *Pharmacology, Biochemistry and Behavior,* 2:487-491, 1974.
33. Ferraro, D.P.; Gluck, J.P.; and Morrow, C.W. Temporally related stimulus properties of delta-9-tetrahydrocannabinol in monkeys. *Psychopharmacologia,* 35:305-316, 1974.
34. Ferraro, D.P., and Grilly, D.M. Lack of tolerance to delta-9-tetrahydrocannabinol in chimpanzees. *Science,* 179:490-492, 1973.
35. Ferraro, D.P., and Grilly, D.M. Marihuana extract in chimpanzees: Absence of long-term effects on operant behavior. *Psychological Reports,* 32:473-474, 1973.
36. Ferraro, D.P., and Grilly, D.M. Effects of chronic exposure to delta-9-tetrahydrocannabinol on delayed matching-to-sample in chimpanzees. *Psychopharmacologia,* 37:127-138, 1974.
37. Ferraro, D.P.; Grilly, D.M.; and Grisham, M.G. Delta-9-tetrahydrocannabinol and delayed matching-to-sample in chimpanzees. In: *Drug Addiction,* vol. III, edited by Singh, J.M., New York: Futura, in press.
38. Ferraro, D.P., and Grisham, M.G. Tolerance to the behavioral effects of marijuana in chimpanzees. *Physiology and Behavior,* 9:49-54, 1972.
39. Fetterolf, D.J., and Ferraro, D.P. Effects of delta-9-tetrahydrocannabinol on the successive discrimination performance of rats. Presented at the Rocky Mountain Psychological Association, Denver, 1974.
40. Fried, P.A., and Husband, C.A. Depth perception in rats following acute or chronic injections of D1-delta-9-tetrahydrocannabinol. *Life Sciences,* 12:289-295, 1973.
41. Fried, P.A.; and Nieman, G.W. Inhalation of cannabis smoke in rats. *Pharmacology, Biochemistry and Behavior,* 1:371-378, 1973.
42. Gluck, J.P., and Ferraro, D.P. Effects of delta-9-THC on food and water intake of deprivation experienced rats. *Behavioral Biology,* 11:395-401, 1974.
43. Gluck, J.P.; Ferraro, D.P.; and Marriott, R.G. Retardation of discrimination reversal by delta-9-tetrahydrocannabinol in monkeys. *Pharmacology, Biochemistry and Behavior,* 1:605-608, 1973.
44. Goldberg, M.E., et al. Effects of delta-9-tetrahydrocannabinol (THC) and chlordiazepoxide (CDP) on state-dependent learning: Evidence for asymmetrical dissociation. *Psychopharmacologia.* 30:173-184, 1973.
45. Gonzalez, S.C.; Karniol, I.G.; and Carlini, E.A. Effect of *Cannabis sativa* extract on conditioned fear. *Behavioral Biology,* 7:83-94, 1972.
46. Greenberg, I.; Kuhn, D.; and Appel, J.B. Dissociation of tolerance to the discriminative and disruptive effects of delta-9-tetrahydrocannabinol, psilocybin and amphetamine. Submitted for publication, 1974.
47. Grilly, D.M., and Ferraro, D.P. Effects of delta-9-tetrahydrocannabinol on delayed matching-to-sample choice speeds in chimpanzees. *Bulletin of the Psychonomic Society,* 2:413-415, 1973.
48. Grilly, D.M.; Ferraro, D.P.; and Braude, M.C. Observations on the reproductive activity of chimpanzees following longterm exposure to marihuana. *Pharmacology,* 11:304-307, 1974.
49. Grilly, D.M.; Ferraro, D.P.; and Marriott, R.G. Longterm interactions of marijuana and behavior in chimpanzees. *Nature,* 242:119-120, 1973.
50. Grisham, M.G., and Ferraro, D.P. Biphasic effects of delta-9-tetrahydrocannabinol on variable interval schedule performance in rats. *Psychopharmacologia,* 27:163-169, 1972.
51. Harris, R.T.; Waters, W.; and McLendon, D. Behavioral effects in rhesus monkeys of repeated intravenous doses of delta-9-tetrahydrocannabinol. *Psychopharmacologia,* 26: 297-306, 1972.
52. Harris, R.T.; Waters, W.; and McLendon, D. Evaluation of reinforcing capability of delta-9-tetrahydrocannabinol in rhesus monkeys. *Psychopharmacologia,* 37:23-29, 1974.
53. Henriksson, B.G., and Jarbe, T. Cannabis-induced vocalization in the rat. *Journal of Pharmacy and Pharmacology,* 23:457-458, 1971.
54. Henriksson, B.G., and Jarbe, T. Delta-9-tetrahydrocannabinol used as a discriminative stimulus for rats in position learning in a T-shaped water maze. *Psychonomic Science,* 27:25-26, 1972.
55. Hirschhorn, I.D., and Rosencrans, J.A. Morphine and delta-9-tetrahydrocannabinol: Tolerance to the stimulus effects. *Psychopharmacologia,* 36:243-253, 1974.
56. Hollister, L.E. Hunger and appetite after single doses of marihuana, alcohol and dextroamphetamine. *Clinical Pharmacology and Therapeutics,* 12:44-49, 1971.
57. Houser, V.P. The effects of delta-9-tetrahydrocannabinol upon fear motivated behavior in squirrel monkeys. *Physiological Psychology,* in press.
58. Izquierdo, I., and Nasello, A.G. Effects of cannabidiol and of diphenylhydantain on the hippocampus and learning. *Psychopharmacologia,* 31:321-332, 1973.
59. Jaffe, P.G., and Baum, M. Increased resistance to extinction of an avoidance response in rats following the administration of hashish resin. *Psychopharmacologia,* 20:97-102, 1971.
60. Jarbe, T.U.C., and Henriksson, B.G. Open-field behavior and acquisition of discriminative response control in delta-9-THC tolerant rats. *Experientia,* 29:1251-1253, 1973.
61. Jarbe, T.U.C., and Henriksson, B.G. Acute effects of two tetrahydrocannabinols (delta-9-THC and delta-8-THC) on water intake in deprived rats: Implications for behavioral studies of marihuana compounds. *Psychopharmacologia,* 30:315-322, 1973.
62. Jarbe, T.U.C., and Henriksson, B.G. Effects of delta-8-THC and delta-9-THC on the acquisition of a discriminated positional habit in rats. *Psychopharmacologia,* 31:321-332, 1973.
63. Jarbe, T.U.C., and Henriksson, B.G. State dependent learning with tetrahydrocannabinols and other drugs. *Ciencia E Cultura,* 25:752, 1973.
64. Jones, B.C., et al. Effects of (-)-delta-9-trans-tetrahydrocannabinols on social behavior of squirrel monkey dyads in a water competition situation. *Psychopharmacologia,* 37: 37-43, 1974.
65. Kalant, A.; LeBlanc, A.E.; and Gibbons, R.J. Tolerance to, and dependence on, some non-opiate psychotropic drugs. *Pharmacology Review,* 23:135-191, 1971.
66. Kaymakcalan, S. Physiological and psychological dependence on THC in rhesus monkeys. *In: Cannabis and Its Derivatives,* edited by Paton, W.D.C., and Crown J., London: Oxford University Press, 1972.

67. Kaymakcalan, S.; Turker, R.K.; and Turker, M.N. Analgesic effect of delta-9-tetrahydrocannabinol in the dog. *Psychopharmacologia*, 35:123-128, 1974.

68. Kelley, J.F., and Hake, D. An extinction-induced increase in aggressive responses with humans. *Journal of the Experimental Analysis of Behavior*, 14:339-348, 1970.

69. Kilbey, M.M.; Forbes, W.B.; and Olivetti, C. Delta-9-tetrahydrocannabinol: Inhibition of deprivation and carbacol-induced water consumption in the rat after central and peripheral administration. *Behavioral Biology*, 8:679-685, 1973.

70. Kilbey, M.M.; Moore, J.W.; and Hall, M. Delta-9-tetrahydrocannabinol induced inhibition of predatory aggression in the rat. *Psychopharmacologia*, 31:157-166, 1973.

71. Kosersky, D.S.; McMillan, D.E.; and Harris, L.S. Delta-9-tetrahydrocannabinol and 11-hydroxy-delta-9-tetrahydrocannabinol: Behavioral effects and tolerance development. *Journal of Pharmacology and Experimental Therapeutics*, 189:61-65, 1974.

72. Kubena, R.K., and Barry, H. III. Stimulus characteristics of marijuana components. *Nature*, 235:397-398, 1972.

73. Leite, J.R., and Carlini, E.A. Failure to obtain "cannabis-directed behavior" and abstinence syndrome in rats chronically treated with *Cannabis sativa* extracts. *Psychopharmacologia*, 36:133-145, 1974.

74 Lyons, J. et al. Effects of delta-9-tetrahydrocannabinol on stimulus control. *Bulletin of the Psychonomic Society*, 2:302-304, 1973.

75. Maker, H.S.; Khan, M.A.; and Lehrer, G.M. The effect of self-regulated delta-9-tetrahydrocannabinol consumption on pregnant mice and offspring. *Federation Proceedings*, 33:540, 1974.

76. Manning, F.J. Acute tolerance to the effects of delta-9-tetrahydrocannabinol on spaced responding in rhesus monkeys. *Pharmacology, Biochemistry and Behavior*, in press.

77. Manning, F.J. Tolerance to effects of delta-9-tetrahydrocannabinol (THC) on free-operant shock avoidance. *Federation Proceedings*, 33:481, 1974.

78. Marriott, R.G., and Ferraro, D.P. Effects of delta-9-THC on inhibitory stimulus control in pigeons. Presented at the Southwestern Psychological Association, El Paso, 1974.

79. McMillan, D.E. Drugs and punished responding I: Rate depending effects under multiple schedules. *Journal of the Experimental Analysis of Behavior*, 19:133-145, 1973.

80. McMillan, D.E. Behavioral pharmacology of the tetrahydrocannabinols. *In: Recent Advances*, edited by Dews, P.B., in press.

81. McMillan, D.E., and Dewey, W.L. On the mechanisms of tolerance to delta-9-THC. *In: Current Research in Marijuana*, edited by Lewis, M.F., New York: Academic Press, 1972.

82. McMillan, D.E.; Dewey, W.L.; and Harris, L.S. Characteristics of tetrahydrocannabinol tolerance. Annals of the *New York Academy of Sciences*, 191:89-99, 1971.

83. McMillan, D.E., et al. Blood levels of ^{3}H-delta-9-tetra hydrocannabinol and its metabolites in tolerant and nontolerant pigeons. *Biochemical Pharmacology*, 22:383-397, 1973.

84. Merari, A.; Barak, A.; and Plaves, M. Effects of delta-1-(2)-tetrahydrocannabinol on copulation in the male rat. *Psychopharmacologia*, 28:273-276, 1973.

85. Miczek, K.A., and Barry, H.III. Delta-9-tetrahydrocannabinol and aggressive behavior in rats. *Behavioral Biology*, 11:261-267, 1974.

86. Miller, L.L., and Drew, W.G. Impairment of latent learning in the rat by a marihuana component. *Nature*, 8:421-426, 1973.

87. Miller, L.L., and Drew, W.G. Cannabis: Review of behavioral effects in animals. *Psychological Bulletin*, 81:401-417, 1974.

88. Miller, L.L.; Drew, W.G.; and Joyce, P. Delta-9-THC: Effect on acquisition and retention of a one-trial passive avoidance response. *Behavioral Biology*, 8:421-426, 1973.

89. Miller, L.L.; Drew, W.G.; and Wikler, A. Comparison of delta-9-THC, LSD-25 and scopolamine on non-spatial single alternation performance in the runway. *Psychopharmacologia*, 28:1-11, 1973.

90. Newman, L.M.; Lutz, M.P.; and Domino, E.F. Delta-9-tetrahydrocannabinol and some CNS depressants: Evidence for cross tolerance in the rat. *Archives Internationale Pharmacodynamie*, 207:254-259, 1974.

91. Olson, J., and Carder, B. Behavioral tolerance to marihuana as a function of amount of prior training. *Pharmacology, Biochemistry and Behavior*, 2:243-247, 1974.

92. Pandina, R.J., and Musty, R.E. Effects of delta-9-tetrahydrocannabinol on retention of a passive avoidance response in rats. *Proceedings of the American Psychological Association*, 993-994, 1973.

93. Parker, J.M.; and Dubas, T.C. Automatic determination of the skin threshold to electroshock and the effects of delta-9-THC. *International Journal of Clinical Pharmacology, Therapy and Toxicology*, 7:75-81, 1973.

94. Pickens, R.; Thompson T.; and Muchov, D. Cannabis and phencyclidine self-administration by animals. Presented at Bayer Symposium on Psychic Dependence, Grosse Sedder, 1972.

95. Potvin, R.J., and Fried, P.A. Acute and chronic effects on rats of (-)-delta-1-trans-tetrahydrocannabinol on unlearned motor tasks. *Psychopharmacologia*, 26:369-378, 1972.

96. Robichaud, R.C., et al. Effects of delta-9-tetrahydrocannabinol (THC) on several rodent learning paradigms. *Pharmacology*, 10:1-11, 1973.

97. Sjoden, P.O.; Jarbe, T.U.C.; and Henriksson, B.G. Effects of long term administration and withdrawal of tetrahydrocannabinols (delta-8-THC and delta-9-THC) on open field behavior in rats. *Pharmacology, Biochemistry and Behavior*, 1:243-249, 1973.

98. Sjoden, P.O.; Jarbe, T.U.C.; and Henriksson, B.G. Influence of tetrahydrocannabinols (delta-8-THC and delta-9-THC) on body weight, food, and water intake in rats. *Pharmacology, Biochemistry and Behavior*, 1:395-399, 1973.

99. Snyder, E.W., et al. Lack of behavioral tolerance to delta-9-tetrahydrocannabinol in stump-tailed macaques. *Proceedings of the American Psychological Association*, 995-996, 1973.

100. Stadnicki, S.W., et al. Crude marihuana extract: EEG and behavioral effects of chronic oral administration in rhesus monkeys. *Psychopharmacologia*, 37:225-233, 1974.

101. tenHam, M., and vanNoordwijk, J. Lack of tolerance to the effect of two tetrahydrocannabinols on aggressiveness. *Psychopharmacologia*, 29:171-176, 1973.

102. Uyeno, E.T. Disruption of maze performance by delta-9-THC. *Proceedings of the American Psychological Association*, 997-998, 1973.

103. Uyeno, E.T. Effects of delta-9-tetrahydrocannabinol on dominance behavior of the rat. *Federation Proceedings*, 32:725, 1973.

104. Uyeno, E.T. Delta-9-tetrahydrocannabinol and the competitive behavior of the rat. *Federation Proceedings*, 33:540, 1974.

105. Wagner, M.J., et al. Effects of delta-9-tetrahydrocannabinol and ethyl alcohol on adjunctive behavior and the lateral hypothalamus. *Physiology and Behavior*, 10:109-132, 1973.

4 Effects in Man

Acute Effects

To clarify certain biochemical, physiological, and psychological aspects of marihuana use, studies on the acute effects of marihuana and its major ingredients have been continued since the last report. A variety of studies employing sophisticated methodology and exploring new research patterns have been conducted for the purpose of assessing the pharmacological activity of cannabinoids of natural, metabolic, or synthetic origin.

The Activity of Natural Cannabinoids

Besides its major psychoactive component, delta-9-THC, natural marihuana contains dozens of other cannabinoids which may have effects of their own or which may contribute to or modify the effects of delta-9-THC. A part of the lore of cannabis use is that different clinical effects are produced depending upon the origin of the cannabis. As more pure marihuana constituents become available for investigative purposes, the role of each constituent is being studied and reported (47, 49, 50, 58).

Besides delta-9-THC, the two most abundant cannabinoids are cannabidiol (CBD) and cannabinol (CBN). Both of these materials, as well as cannabichromene, cannabigerol, and cannabicyclol have been found to be inactive in monkeys and did not alter the response of these animals to doses of delta-9-THC given concurrently (80). A study performed with six normal, experienced human volunteers confirmed the preclinical findings; namely, that CBD and CBN lacked pharmacological activity. Hollister (47) gave oral doses of CBD or CBN to six normal, experienced volunteers beginning with a 20 mg dose of delta-9-THC, which shows definite but moderate effects in man. Doses were raised progressively until at least one subject received a maximum dose of 400 mg of CBN and another, 100 mg of CBD. The latter compound was given intravenously as well as orally to four subjects, in doses ranging from 5 mg (considered a very potent i.v. dose of delta-9-THC) to 30 mg. All doses were without any discernible effects; none of the characteristic mental effects of cannabis were observed, and there was a complete absence of any change in pulse rate, or degree of conjunctival reddening of the eyes.

While the lack of pharmacological activity was confirmed in the human study above, the question of whether CBD or CBN can interact with delta-9-THC is still unresolved. For example, in an extensive laboratory study of two different samples of cannabis the differences in response to the samples could not be explained solely on the basis of their delta-9-THC content (16). The effects of one of the samples of cannabis tested in both animals and human subjects with psychological tasks and physiologic measures were approximately two-to-four times greater than would be expected based solely on THC content. The authors suggest that a cannabinol and delta-9-THC interaction accounts for the differences. In another study comparing the effects of chronic administration of 200 mg THC daily to hospitalized volunteers the effects are greater when the THC is given as a hashish extract rather than when administered as pure THC in sesame oil (57). Although the subjects knew the nature of the drug, they did not know the dose or the specific constituent administered in one of a series of three trials. The spectrum of the somatic, perceptual, and psychological effects observed was qualitatively similar for both isomers, but the potency of delta-8-THC was considered to be only 75 percent that of the delta-9-THC. The estimated ratio of potency for intravenous doses given to four volunteer subjects was exactly the same as for the oral doses (50).

Another group of investigators (58) compared the same two isomer THC's on five volunteer subjects. When smoked, they found delta-9-THC nearly twice as active as delta-8-THC in inducing psychological effects. Qualitatively there was no detectable difference between the effects of the two isomers.

Tetrahydrocannabidivarin, a propyl side chain homolog of delta-9-THC, has been isolated from a number of different types of marihuana. Although it is rarely the major constituent in some cannabis variants, it may represent 20-30 percent of the cannabinoids present. When six subjects were given intravenous doses of 7 mg of delta-9-tetrahydrocannabidivarin, all but one subject had mild to moderate effects similar in most respects to those experienced from delta-9-THC (49). From these results, one would estimate the potency of this compound to be 25 percent that of delta-9-THC. Thus, it appears that changes in molecular structure within the series reduce potency but do not appreciably alter the qualitative effects of the material.

The Activity of Delta-9-THC Metabolites

The activity of various monohydroxylated metabolites of delta-9-THC has been studied by three independent groups of investigators (49, 68, 99).

11-hydroxy-delta-9-THC, claimed to be a major metabolite of delta-9-THC, has been found to be active by all three groups using intravenous administration of the drug. However, because of differences in the rate of administration, the dosage given and the evaluation techniques utilized, disagreement exists among the three groups as to the activity of this metabolite relative to its parent compound. At issue is Lemberger's contention that delta-9-THC is acting via conversion in the body to a more potent metabolite (68). The data so far available do not allow us to draw a definite conclusion in this matter.

Two other relatively minor metabolites have been subject to clinical investigation (49, 99). 8-beta-hydroxy-delta-9-THC has been found to be active by two groups of investigators, but its activity was definitely less than that of delta-9-THC. The 8-alpha-hydroxy-metabolite of delta-9-THC was found by Hollister (49) to be slightly more active than the 8-beta-hydroxy, while Perez-Reyes et al. (99) found it completely inactive. Again, methodological differences may account for these discrepancies in findings.

The 11-hydroxy metabolite of delta-8-THC has been tested by Hollister in four subjects and found to be slightly more active than its parent compound, delta-8-THC (49).

The Activity of Synthetic Cannabinoids

The pharmacological activity of some synthetic cannabinoids has also been investigated (53, 69, 109).

In an extensive series of investigations several decades ago (2, 3) a number of compounds differing molecularly from the naturally occurring tetrahydrocannabinol (THC) were synthesized. One of these compounds, synhexyl (essentially delta-6a-10a-THC with a hexyl rather than an amyl side chain) had been used clinically in the late 1940's and early 1950's (45, 95, 119). Hollister et al. (53) described extensively the clinical syndromes from synhexyl and natural delta-9-THC—including their time course—as well as some physiological, psychological, and biochemical effects. Both THC isomers produced clinical syndromes identical to those produced by eating hashish but with an estimated potency ratio of 3:1 (delta-9-THC over synhexyl). Another major difference was that the effects of synhexyl were slower in onset and of longer duration than those of THC, suggesting slower metabolism. This study indicated that the position of the double bond in the unsaturated alicyclic ring and/or the length of the alicyclic side chain might alter the potency of the compound but would not markedly alter its pharmacological action.

Some delta-6a-10a-THC (with the natural amyl rather than hexyl side-chain structure), the material which for many years had been considered the active component of cannabis, was obtained (49). To test the material, it was added to a tobacco cigarette and although the smoking of even a regular cigarette in the manner used by marihuana smokers was adequate to produce a transient high, the effects from the three cigarettes containing the active materials were distinctly different. All showed clear resemblance to the effects obtained from marihuana; the delta-9-THC smoke was estimated as three to six times more potent than the other two. A previous study of smoked delta-6a-THC, using doses almost twice as large as Hollister had used, failed to reveal activity for this compound (56). The source of the presently used material was different, which might have accounted for the different results. In any case, it proved that delta-9-THC is indeed the active component of hashish.

An early clinical trial of the most potent related compound, dimethylheptyl-delta-6a-10a-tetrahydrocannabinol (DMHP), indicated that this compound might be useful in the therapy of grand mal epilepsy not readily amenable to treatment by other drugs (27). Further investigations were terminated because the potency of the available preparation varied from one sample to the next.

As the compound has three asymmetric carbon atoms, it can exist as eight optical isomers, and differing proportions of these isomers occurring in different samples may explain the inconsistent activity found. Since then, these isomers have been isolated and Sidell et al. (109) recently reported their effects in man. The main effect observed in this study was hypotension, most prominent when the subjects were in a standing position. In the doses used, isomers identified as "2" and "4" (and their mixtures) were the only ones possessing biological activity. Doses of between 1 and 2 mg/kg produced a pronounced and prolonged orthostatic hypotension. Tachycardia occurred even while the subjects were at rest with isomer "4." Symptoms related to hypotension in addition to dry mouth, thirst, hunger, sleepiness, and irritated eyes with conjunctivitis suggested a mild marihuana syndrome.

These effects of DMHP have been confirmed by Lemberger et al. (69) who used C14-labeled DMHP, which allowed them to investigate the metabolic disposition of the compound in man.

Metabolism and Biochemical Effects

As would be expected from its marked lipid soluble nature, delta-9-THC is a good substrate for the hepatic microsomal enzymes. In addition, it is also a potent in vitro inhibitor of the biotransformation of other drugs which are metabolized by the liver microsomal enzyme systems. Therefore, it is of considerable interest to study the in vivo metabolism, disposition, and pharmacodynamics of delta-9-THC and other cannabinoids in man (49, 70, 76).

The metabolic problems of delta-9-THC described in some detail in the last *Marihuana and Health* Report were partly based on unpublished work then sponsored by the National Institute of Mental Health. Some of this work has now appeared in print (68, 97).

New data, showing that not only delta-9-THC but also its active metabolite (11-hydroxy-delta-9-THC) is tightly bound to human plasma protein, have been published (126). These data suggest that in addition to the lung, spleen, and fatty tissues, the plasma proteins of the blood may serve as a depot for delta-9-THC and its hydroxylated metabolite.

Some other cannabinoids have also been investigated from the metabolic point of view. Hollister had studied the urinary excretion of cannabinoid metabolites after oral administration of cannabidiol or cannabinol (51). Using thin layer chromatography, he found both cannabidiol and cannabinol (unlike THC) largely unchanged when excreted. This difference in metabolism might be the reason that these two cannabinoids were found to be pharmacologically inactive in man (e.g., 47).

The question of whether cannabidiol, when smoked, becomes a THC has been investigated by Quarles et al. (100). Cyclization apparently depends on the conditions. It was found that cannabidiol does not form delta-9-THC when marihuana cigarettes are smoked by a human subject, nor by a smoking machine. On the other hand, cannabidiol applied to tobacco cigarettes (which provide a hot, wet acidic substrate) has been shown to be converted partially to delta-9-THC when the cigarettes are machine smoked (100). This is consistent with earlier reports that this conversion may occur with certain acid-catalyzed circumstances.

The studies on the metabolism of the synthetic cannabinoid 14-C-DMHP indicate that the excretion pattern of DMHP appears to be different from that of delta-9-THC. In contrast to THC, where as much as 30 percent is found in the urine, the majority of the C-DMHP compound is excreted in the feces (69). Preclinical reports on the interaction of delta-9-THC with biogenic amines have been highly conflicting: even after high doses only slight changes could be demonstrated in the metabolism or turnover of biogenic amines, and species differences among the experiments cast doubt as to the generality of these findings. (See section 2 on Preclinical Research.) Pharmacologically active doses of delta-9-THC in man produced little demonstrable changes in excretion of catecholamines, serotonin, or their metabolites (49, 84).

Alphamethylparatyrosine (AMPT) is an effective inhibitor of tyrosine hydroxylase, the rate-limiting step in the synthesis of catecholamines. Although pretreatment with doses of 2 and 4 mg of AMPT can block the euphoric effect of 200 mg dl-amphetamine, similar pretreatment failed to block the typical psychological effects of 20 mg of orally administered delta-9-THC in 10 subjects (48). Some slight accentuation of the total intensity of clinical effects from THC was apparent in these experiments, but one could not ascertain whether this difference was due to additive pharmacological effects of AMPT plus THC or diminished catecholamine concentrations in the brain. It would appear that mental effects of THC are not mediated primarily through changes in brain concentrations of catecholamines alone but rather by the balance between these amines and others such as acetylcholine or serotonin.

The interaction of marihuana with other commonly used or abused drugs has not been studied on the metabolic level in man, although such interactions are fairly well documented in animals, and interaction at the psychological level has been demonstrated in man (9, 101, 102, 127).

Physiological Effects

Researchers have attempted to focus more clearly on the reports of marihuana's effects on peripheral physiological function since the last report was developed. Potentially significant cardiovascular effects from cannabis use have been described (6).

The electrocardiograms (EKG's) of seven young men were studied by Kochar and Hosko (63) after oral administration of placebo and two doses of delta-9-THC (200 mg/kg and 300 mg/kg) given to each subject at 3-day intervals. After a small dose of THC, only two of the seven subjects showed EKG changes, but after a larger dose, six manifested increased heart rate, two developed S-T segment and T-wave changes, and one had premature ventricular contractions. No EKG changes occurred after the placebo was administered. Marihuana may affect the heart and the repeated use may have a cumulative effect, the authors concluded (63). However, other studies using smoked cannabis report less consistent EKG changes—or no changes at all (29, 106).

In an editorial of the *Journal of the American Medical Association*, where the report appeared, editors expressed concern that cardiovascular involvement may, indeed, be a cumulative effect of marihuana use. But the editorial was quick to caution that, ". . . for the moment, however, taking a short range view, we can see greater danger in overreading the EKG of cannabis users and misdiagnosing coronary disease or pericarditis where none exists" (30).

In a letter to the editor of the same journal, Wendkos (125) called attention to the clinical experience that S-T elevation and T-wave lability is a benign EKG syndrome frequently found in healthy individuals and thought to be a manifestation of responsiveness to sympathetic stimulation. In the reported cases, the EKG changes can be related merely to the recognized sympathomimetic action of cannabis, and not, as the authors have suggested, to adverse myocardial effects.

In another study, 10 normal men in their 20's smoked marihuana cigarettes or placebo cigarettes on separate experimental days while their EKG's were continuously recorded (106). Automated methods of data analysis were used to scan the EKG records for cardiac arrhythmias and to plot graphs of pulse rate and average T-wave amplitudes. Only five ventricular premature contractions occurred in all of the sessions, and they were not related to marihuana intoxication. T-wave changes were slight and did not correspond to the marihuana effect. In light of these findings and the relevant literature, the authors suggested that syncopal episodes associated with marihuana intoxication are not associated with cardiac arrhythmias, but rather with orthostatic or vasovagal reactions combined with inhibition of compensatory vascular reflexes. A single case report of what was probably the "ingestion" of a large dose of hashish extract reported no EKG changes (75).

Marihuana effects may be different in people with disease. This is well illustrated by a study of the effect of smoking marihuana and placebo on angina pectoris (4). Ten patients with angina pectoris and documented coronary artery disease smoked a portion of a marihuana cigarette containing 20 mg of THC. The patients experienced angina after exercise sooner and after less work after smoking the marihuana. Smoking the placebo produced a similar but smaller change in exercise tolerance. Their EKG's showed similar ischemic S-T segmented depression in all conditions, but they occurred earlier and after less exertion after smoking marihuana. The authors surmised that cannabis probably increased myocardial oxygen demand and decreased myocardial oxygen delivery.

The question whether marihuana can alter the physiological responsivity to stressful situations has been investigated by Rickles et al. (104). Ten volunteer male subjects were randomly assigned in equal numbers to placebo or marihuana groups under double blind conditions. After instrumentation for EKG, galvanic skin response, and forearm blood flow, 10 minutes of baseline physiology were recorded followed by 10 minutes of stress (mental arithmetic with experimenter harassment) and another 10-minute resting period. After smoking two cigarettes with either placebo or natural marihuana containing 14 mg of delta-9-THC, the baseline, stress, baseline sequence was repeated.

The results of this experiment indicated that moderately high doses of marihuana do not impair physiological reactivity as measured by heart rate and forearm blood flow responsivity to a psychological stress.

The study on the pulmonary physiological effects of smoked marihuana and oral delta-9-THC by Tashkin et al. (118) mentioned in the third *Marihuana and Health* Report has now appeared in print. The bronchodilating effects of marihuana smoking have also been reported by another research team headed by Vachon (121). (See section 5 on Therapeutic Aspects.)

Endocrine and Metabolic Effects

Relatively little work has been published to date on endocrine system changes produced by cannabis. There is, however, increasing evidence that hormonal activity in humans may be altered by cannabis.

In a study by Kolodny et al. (64) blood levels of the male hormone testosterone were significantly lower in a group of 20 young marihuana smokers than in a comparative nonmarihuana-using control group. Of the users, six had reduced sperm counts and two were impotent, apparently comparable with their frequency of use. However, upon cessation of marihuana use, the testosterone levels promptly returned to normal. The data suggest that central (hypothalamic or pituitary) alterations may be responsible for these effects.

The Kolodny group expressed concern about the possibility of depressed fetal testosterone levels during the critical states of sexual differentiation and its resultant developmental effect (64). However, another group (83) found no depression of testosterone concentrations in the blood in a group of heavy cannabis users who smoked cigarettes chronically while living on a controlled research ward. They suggest that Kolodny's findings may result from use of other drugs in his outpatient population. A third group (22) studying cannabis users smoking heavily in a similar research ward setting has confirmed the Kolodny group observation. There is no obvious explanation for the discrepancy in findings in the two research ward settings. The possible effects of hypothalamic or pituitary suppression in the prepubescent male user is also a source of concern. The biological significance of lowered plasma testosterone levels is not fully understood. Thus, any predictions as to the consequences are, at best, speculative. The Kolodny findings do, however, suggest that the anecdotal accounts of heightened sexual drive associated with marihuana use may not be accurate.

Although marihuana is often thought to produce symptoms of hypoglycemia, studies reviewed in previous years indicate fasting blood glucose levels are unaffected by various doses of marihuana. A recent study suggests that, in fact, marihuana may have the opposite effect and actually produce a diabeticlike glucose tolerance response (52). Intravenous doses of 6 mg of THC were given to casual marihuana users prior to an oral glucose tolerance test and, when compared to the control situations, five of the six subjects had elevated blood glucose values. Plasma insulin level showed no difference between treatments, while growth hormone levels rose following the glucose load after THC. The changes suggested that resistance to the action of the insulin was responsible for the glucose intolerance. A similar group of subjects smoked a cigarette containing 19 mg of THC and evidenced no such changes in glucose tolerance, suggesting that the phenomenon is related to the relatively higher dose administered intravenously. The rarity of observed diabetagenic effects from marihuana might be due to either the low dose usually consumed or to the development of tolerance to such effects, Hollister and Reaven thought (52).

Examining a related aspect of endocrine response, an insulin tolerance test was administered to a group of six subjects before and during a period of chronic high dose of oral THC ingestions (57). The 10 days of THC administration did not seem to alter the expected response to insulin with respect to blood glucose, ACTH, and cortisol changes. However, the expected increase in growth hormone after insulin was completely blocked.

Neurological Effects

Several studies of neurological effects described in the third *Marihuana and Health* Report have now been published (34, 55, 111, 123). Some additional work on electroencephalographic (EEG) correlates of attentional processes while under the influence of marihuana has also been completed in the interim.

In one study constant alerting procedures were employed with computerized data acquisition and analysis to study the effects of smoked marihuana or oral doses of THC on various parameters of the EEG and on other physiological measures. Some minor, diphasic, task-related shifts in the EEG frequencies and in the mean-evoked heart rates have been found in these experiments (74). Kopell et al. (65) have studied the amplitude of the contingent negative variation (CNV) in the EEG of 12 subjects receiving placebo and quantified "social" doses of THC and alcohol in a double-blind design. It was found that THC selectively enhanced the amplitude of CNV as compared to placebo while alcohol depressed it. Since the CNV amplitude is fundamentally associated with attention-related behavior, the authors interpreted their findings as an objective measure of the subjects' increased ability to selectively "tune out" the outside world. The opposite effects of alcohol on this CNV measure are interpreted as a result of a probably more generalized suppressive action of alcohol on arousal produced by the reticular formation of the brain stem.

Canadian investigators (76) have confirmed these EEG changes after administration of marihuana to 75 healthy, young adults. Smoked marihuana, in doses of 9.1 mg THC, induced a significant decrease in the peak power of the alpha rhythm and a slight increase in auditory-evoked response latency. The CNV increased in amplitude and sequential CNV's showed changes consistent with sustained attention but decreased certainty about performance on a discrimination task. The authors, in interpreting the meaning of their data, speculate that, "Cannabis drugs may allow the individual to exist at a phylogentically old mammalian level literally within the emotional brain itself, free from the conflict which is constant between the old sensory and feeling-oriented system and the newly imposed civilization brain" (76). Further, the authors point out that such "regression in service of the ego is not new in our society, nor is it unique to the marihuana experience" (76). It is practiced regularly in such culturally approved forms as alcohol consumption, the use of tranquilizers, and in some of our acculturated rituals and ceremonies.

There are still only tentative findings regarding the relationship of cannabis use to sleep EEG. There are no clear reports on the ability of ordinary social doses of marihuana to alter sleep EEG patterns.

A study on high dose, chronic use of the drug (33) showed a large decrease in rapid eye movement (REM) sleep.

A different pattern of sleep EEG effects was noted in 12 outpatients smoking 0.2 mg/kg of THC before bedtime (5). The most marked change was a decrease in slow wave sleep lasting through the 10 days of daily drug administration. REM sleep was not changed by the cannabis. The authors suggest that the apathy, lethargy, and less competitive lifestyle reported to be associated with cannabis usage may be related to the slow wave sleep suppression. The great discrepancy in the findings of these two studies may be related to dose or methodologic differences. In any event, the sleep EEG seems to be a sensitive indicator of cannabis effects (23). (See section 5 on Therapeutic Aspects.)

Effects on Mental and Motor Performance

Further studies in the past year confirmed the findings reported in the last *Marihuana and Health* Report that marihuana impairs short-term memory processes in the brain (18, 24, 26, 36, 102, 120, 124). A variety of cognitive tests—Digit Recall, Addition and Subtraction, Free Association, Running Memory Span, etc.—and psychomotor tests—Simple and Complex Reaction Time, Continuous Performance Test, Time Production, Goal Directed Serial Alternation, Finger Labyrinth Test, Trail Making, Concept Formation, etc.—were used by these investigators.

One group found that memory impairment appears to consist of a difficulty in transferring information from short-term memory to longer term memory store, but retrieval of information which had been stored in memory before ingestion of the drug is not affected (24, 25, 26, 44). Others think the defect is in short-term recognition memory (128). This memory impairment seems to be related in some way to a faster internal tempo during marihuana intoxication, also well documented by research (19, 120). A study considering the effects of 15 and 23 mg oral doses of THC reported effects on memory and information processing and attempts to use an impaired attention model to account for memory impairment (28). The state dependency of the memory impairment has also been demonstrated and has been suggested to be related to the abuse potential of marihuana (43, 105, 115, 116). The phenomenon of state dependence has been demonstrated for a variety of drugs such as alcohol, stimulants, and barbiturates. These neuropsychological effects of marihuana have been confirmed by Canadian workers in both male and female subjects (62). The investigators reported only minor differences between male and female subjects in their responses to marihuana as measured by the various psychological tests.

Effects on Sensory Function

Diminished thermal discrimination following administration of 15 mg oral THC has been found, which suggests that marihuana has some analgesic properties (128). However, a study using a much larger subject sample smoking approximately 12 mg of THC showed increased sensitivity to both painful and nonpainful electric stimulation of the fingers (43). (See section 5 on Therapeutic Aspects.)

An investigation of the effects of 0, 100, and 200 µg/kg of smoked THC on the psychological refractory period produced results which were difficult to interpret. They seemed to suggest that cannabis effects are unrelated to refractory phenomena but may be related to slowed central processing of information (87).

That the sensory effects of cannabis are complex is further indicated by a study that found increased sensitivity to electrical stimuli and decreased light flicker fusion frequency (42, 108). This would suggest, at least at the dose studied (12 mg THC), that cannabis has a stimulating effect on the central nervous system. This is not completely consistent with other perceptual-motor task data which suggest depressant effects. For example, one report described vestibular function in a mixed group of frequent cannabis users (112). Another brief clinical report on opthalmology suggested mixed stimulant-depressant actions (122).

Driver Performance

Interest in evaluating the effects of cannabis on automobile driving behavior or on simulated driving tasks continues (18, 59, 73, 101). Oral doses of cannabis resin containing 8, 12, and 16 mg of THC were compared to a 70 g dose of ethanol on a simulated driving task (101). Both drugs increased braking and starting times. Cannabis decreased the number of gear changes while alcohol increased them. Otherwise, the drugs were very similar in their effects on the performance tasks. Two other studies used laboratory tasks presumably related to driving skills. In one, marked impaired attention and concentration after large oral doses of THC (up to 28 mg) were found (59). The other study noted a decrement in performance on a divided attention task similar to that found after alcohol intoxication following administration of 3 or 6 mg of smoked THC.

A recent Canadian study (61) attempted to evaluate the effects of marihuana both in low and higher social doses (cigarettes containing 4.90 mg and 8.40 mg of THC respectively) on performance in a driving course situation and under traffic conditions in a large city. Performance was rated on the basis of the ability to negotiate the course without displacing a series of cones, judgment in avoiding entering a portion of the course too small for passage without displacing cones, and the time required for emergency braking. In the traffic situation driving was assessed based on the scoring system used by the Provincial Department of Motor Vehicles in rating drivers being examined for licensing. A double-blind procedure was employed in which neither drivers nor scorers knew who had received active drug materials or placebo. While not all drivers were affected, significant mean declines in the rate of improvement on the driving course performance were noted in both low- and high-dose groups. In the traffic situation a significant decline in performance was noted for the higher dose groups but not for those receiving a lower dose. The author concludes, "Driving under the influence of marihuana should be avoided as much as should driving under the influence of alcohol." In view of the frequency with which alcohol and marihuana are used in combination (64 percent of the sample reported having used alcohol in combination with marihuana prior to driving in the past), the author goes on to stress the need for further study of the effect of these drugs used simultaneously under conditions as closely approximating normal driving as possible.

Factors in Marihuana Self-Administration

Because of the social characteristics of marihuana use, there has been some interest in the factors that control the self-administered dose when smoking (13, 14, 15, 29). In experiments where subjects smoked to an "optimal high" it appeared that variables such as physical size of cigarettes and other harder to define nonpharmacologic variables were more important in determining the dose consumed than the potency as judged by THC content (13, 15, 29). The studies demonstrated that the term "usual social dose" can mean a range of doses from, at minimum, 2 or 3 mg upwards to 18 mg of THC. At the lower end of the dosage range there was evidence that some subjects could "bring themselves down" from a high at will, at least in performing a time-estimation task. Performance on a memory task was not altered by volitional control (14).

Work Performance

The question of a possible "amotivational syndrome" related to marihuana use has been widely speculated upon. One recent study (82) has objectively measured work performance related to marihuana use in a group of 28 male subjects who volunteered to participate in a study of chronic marihuana use in a hospital setting. During their 31 days participation they were given a simple button-pressing task which could readily be carried on even while participating in other activity. On the basis of their rate of responding, subjects were rewarded by accumulating amounts of money which could be exchanged for marihuana cigarettes during the experiment or redeemed in cash at its conclusion. Generally, marihuana was found to depress work output to an increasing degree at successively higher levels of use. Subjects who were heavy users had a greater decline in work output on the days following use than on the same day of use, while casual users' work output showed a dose-related work decrease on both the same day and the following day. The authors caution that work output and motivation are complexly related to the type of task, the reinforcing consequences, the setting, etc. Thus, it is not yet clear to what extent their experimental findings are applicable to work performance under other conditions.

Chronic Effects

Marked tolerance to the major effects of cannabis is not commonly observed among users in this country. Relatively few direct experimental studies of chronic cannabis administration to humans have been finished and reported so that only inferences are possible at this time. However, there is increasing evidence that tolerance to various effects can develop in man. In all long-term, chronic dose studies, some degree of tolerance was noted to certain clinical effects.

In a free choice study where subjects could select their own dose level each day they gradually increased their consumption of cannabis during the 20-day smoking period (85). In a chronic administration study at the Addiction Research Foundation of Ontario, tolerance to some cannabis effects may have developed (67). When doses were given daily for 1 month, the rate of pulse increase became progressively less to a given dose. No evidence for cumulative effects was noted. A study of oral ingestion of much larger doses of THC (210 mg daily) than used in the above studies showed marked tolerance to many of the usual behavioral, subjective, and physiologic effects of THC after 5 to 10 days on the drug (57). In another study in which lower doses of THC were given to depressed patients the data suggest tolerance to drowsiness in some patients (66). This suggests that the magnitude of tolerance, like so many other drug aspects, depends partially on dose and frequency of administration. This seems to be the case with tolerance in animals.

Studies of outpatients to determine tolerance produce variable results because of the inconsistent and generally lower doses of cannabis consumed in social situations. In one study, a small group of outpatients were given 20 mg of THC orally at bedtime for 5- or 12-day periods (54). Slight tolerance to the THC-produced dizziness and tachycardia was found; progressive fatigue and "grogginess" developed in the course of chronic administration. No sensitization or "reverse" tolerance was noted.

In another study four hospitalized, chronic marihuana users were studied over 16 days and given smoke from 435 mg of marihuana containing 1.5 percent delta-9-THC twice daily (103). Three subjects were given smoke from 2.8 percent cannabis. Some minimal evidence of tolerance was noted in a behavioral task and on posttrial cardiovascular changes, but the results were inconsistent. One subject developed a brief toxic psychosis and another pneumonitis. No obvious withdrawal syndrome was noted.

Another strategy for investigating tolerance is to select groups of subjects who describe varying levels of marihuana use and examine different patterns of response in frequent and less frequent users. Some studies cited in previous reports noted a trend for frequent users to show less response on some measures of marihuana effects, though this has been far from a universal finding in the literature. A number of investigators used this approach in recent publications.

One group compared the performance of frequent users on a verbal learning test that was shown to be sensitive to cannabis-induced deficits in a previous study with infrequent users (21, 105). There was a learning decrement for paired-associate learning observed in the less frequent users, but it was not evident in the sample of chronic frequent users. Also, the drug state dependent learning phenomenon exhibited by the social users did not occur. Most of the frequent users smoked marihuana five to six times a week and went to work or school intoxicated. The light user group was almost exclusively weekend users. A possible pitfall in this strategy, as pointed out by the authors, was that the frequent users were less motivated to perform and less dependable than the lighter users.

Another study found no difference between experienced (one cigarette per week) and cannabis-naive subjects compared by performance on three cognitive tasks (18). Both 3.3 and 6.6 mg doses of smoked delta-9-THC slowed performance equally in both groups on serial seven subtraction and goal-directed serial alternation tasks. Similar quantitative and qualitative subjective effects were reported by both groups. In contrast to earlier reports, digit span performance was not altered by cannabis. One possible difference between this and the preceding study is that the experienced users were certainly not frequent users by Los Angeles standards. Thus, it may be unreasonable to expect tolerance to be evident in a group using cannabis so infrequently. Naive subjects achieved a level of intoxication equal to that of the experienced users. This suggests that the belief that experience is required for the inexperienced user to achieve a high equal to that of the more experienced may be a myth.

The cardiac and subjective effects of delta-9-THC infused intravenously were compared in 15 frequent users who averaged 290 cigarettes per year and 15 infrequent users (99). No significant differences were subjectively perceived nor was the magnitude of the heart rate increase different in the two groups. An additional comparison between a group of eight subjects who used an average of 493 cigarettes per year and one that used three produced similar results. The authors suggest that 493 cigarettes a year for 4 years should be more than enough exposure to any drug to induce the development of detectable tolerance or sensitivity. However, it is uncertain whether a similar assumption would be made based on consuming 493 shots of vodka per year or one sleeping pill per night or one or two nicotine cigarettes per day.

The authors in the preceding study also assume their subjects used good quality cannabis with a high THC content. However, this may not always be true for all cannabis users. For example, a survey of 36 cannabis cigarettes or samples of cannabis resin in London, England, found THC content varied from 0.15 mg to 41 mg of THC (32). Using a technique of participant observation, users were noted to consume from 0.3 to 8.3 g of cannabis daily (with a THC content of 1-88 mg per day). Thus, statements of mean or average amounts of cannabis smoked can be misleading, since frequent use does not always indicate high daily intake of THC.

Although there is occasional discussion of a withdrawal syndrome in the older literature, no published reports have appeared recently. In a report mentioned in an earlier section (Acute Effects—Neurological Effects), a suppression of rapid eye movement sleep during chronic administration of 210 mg doses of THC was followed by a marked REM sleep rebound upon sudden withdrawal (33). Subjective sleep disturbance is repeated by the subjects for weeks following chronic high level dosages. Other aspects of the withdrawal or abstinence syndrome include irritability, restlessness, hyperactivity, decreased appetite, sweating, sudden weight loss by diuresis, increased salivation, increased intraocular pressure, and, in general, many symptoms similar to a sedative-hypnotic type withdrawal syndrome (57). The onset is sudden—6-8 hours after the last dose—and, for the most part, is over in 48 hours except for the more subtle, long-lasting effects. Whether this occurs or can be measured at lower doses is, of course, open to question.

Recent reports on the effects of chronic overseas cannabis use have been limited to psychological assessments, and all such studies were generally unable to demonstrate any adverse sequelae (8, 10, 36, 38, 46). In a controlled study comparing 30 Jamaican chronic cannabis smokers with a history of at least 7 years of daily use with individually matched nonsmokers, Beaubrun and Knight (8) found no significant differences in a number of measures of social and psychological functioning, diagnosed psychopathology, abnormal mental status, criminality, social or economic mobility, or use of other drugs. Smokers did have significantly higher incidence of positive family history of mental illness, but did not themselves have any greater incidence of mental illness than nonsmokers. Since a greater likelihood of mental illness in the subjects would be expected with a positive family history, the authors wonder if cannabis smoking might protect predisposed individuals from psychoses.

In another Jamaican study (10) psychological test performances of 16 adult male cannabis smokers with a history of at least 10 years of daily use were compared to 10 noncannabis-using controls. No indication of impairment could be found in users on measures of memory; physiological, sensory, and perceptual-motor functioning; and concept formation and abstracting abilities. Because of the negative results, the authors then repeated the study on 14 users and 14 controls, using a modified research design to control for variables such as drug potency, literacy, and motivation, which might have affected the original study's outcome. The initial findings were strongly confirmed by the data obtained in the second project, and the authors concluded that "heavy users of cannabis did not show test performances indicating impairment of psychological functioning comparable to other types of organic cerebral dysfunction, nor did they show chronic changes on dimensions response to immediate intoxication" (10). In a paper summarizing the Jamaican cannabis experience Dr. Beaubrun, the senior investigator on the U.S. supported chronic marihuana study done there, made the following observation:

> In contrast to the relatively benign picture of cannabis use among the poor and the dispossessed, we note the tendency for marihuana to cause more problems among the middle class youth even though only a few of them in Jamaica use it. School dropouts, transient psychotic episodes, panic reactions and adolescent behavioral problems have all been observed (7).

Chronic ganja users in Jamaica are predominantly from the lower socioeconomic class, including farmers and fishermen from rural areas and unskilled laborers. It is possible that any subtle intellectual deficits resulting from chronic cannabis use might not have been detected in the original study population and that conclusions drawn may not be applicable to chronic users in the United States.

Several studies of American chronic users have been reported (36, 38, 46). Hochman and Brill (46) surveyed randomly selected students at U.C.L.A. and compared three respondent groups, classified according to marihuana use: (a) individuals using it less than 10 times in the past year were classified as "nonusers" along with abstainers and experimental users; (b) individuals using cannabis from 10 times throughout the year to twice per week for up to 2 years were classified as "occasional users"; and (c) individuals using cannabis 3 or more times per week for 3 or more years or daily for at least 2 years were classified as "chronic users." To control for any self-selection factors between responders and nonresponders to the survey, nonrespondents were compared with respondents for age, sex, race, major, and class standing in addition to drug use history, and it was concluded that whatever moved students not to cooperate was apparently unrelated to these variables. The authors could find no statistical difference between users and nonusers in academic performance, and chronic use seemed to have no effect on motivation, a finding which questions the validity of an "amotivational syndrome," at least in a college population continuously enrolled. In addition, the authors could find "no evidence that preexisting psychopathology, as such, is a significant determinant of marihuana use, including chronic use" (46). (See section on Cannabis and Psychopathology, below.) It should, however, be noted that results in this relatively motivated group may not be characteristic of all segments of the population of users.

Grant et al. (36) administered a large battery of sensitive neuropsychological tests to 29 medical students who had smoked marihuana regularly for at least 3 years with a mean frequency of three times a month and to 29 nonusers of marihuana or any other drugs. Essentially, no differences between the two groups (who were matched for intelligence) were found, and the authors conclude that "moderate social usage of marihuana in this stable group does not result in sufficient impairment of function that it can be detected by the most sensitive neuropsychological instruments now available."

The studies of chronic cannabis users in the United States and Jamaica all come to similar findings—that chronic use does not produce detectable psychological impairment. However, it must be pointed out that both U.S. studies were conducted on selective populations and the actual amount smoked could not be controlled—shortcomings which are probably unavoidable in any retrospective investigation. Longterm followups of the subjects in these studies, if possible, would probably provide valuable data to clarify the question of possible detrimental psychological effects resulting from chronic cannabis use. (See section on Cannabis and Psychopathology, below.)

Effects of Marihuana on Chromosomes and Reproductive Processes

Since the publication of the third *Marihuana and Health* Report, several studies describing chromosome damage attributed to marihuana use have been published. However, two recent conferences convened by the National Institute on Drug Abuse concluded that it is still doubtful whether cannabis is a danger to human genetic and reproductive processes, under the conditions and in the doses commonly used by marihuana smokers. Contradictory data may reflect methodological and sampling differences which hopefully will be clarified by new and ongoing work.

Stenchever et al. (114) presented data from 49 marihuana users (29 males and 20 females) and 20 controls (12 males and 8 females). Peripheral blood lymphocyte cultures were studied to examine chromosome breaks and abnormal forms. An average of 3.4 cells with breaks per 100 cells (range 0-8) were noted in the user group and 1.2 broken cells per 100 cells (range 0-5) were noted in the control group. No significant differences were noted in the increased chromosome breakage between "heavy" and "light" users, users of mixed drugs when compared to users of marihuana only, users of marihuana and caffeine when compared to marihuana users not also using caffeine, and male and female users.

Although this increased rate of breakage was statistically significant, the biological significance of the findings remained unclear because of several methodological and sampling questions raised by the authors themselves. The mechanism of this effect also remains unclear. That delta-9-THC itself did not break chromosomes in vitro was shown by the same authors (113) as well as others (91). Among the "users" as well as the controls there were persons who showed no breaks, and an elevated frequency of breaks has been reported among "users" of all kinds of street drugs. By contrast, there is the example of LSD which, when administered under controlled conditions in known doses of pure compound, failed to produce an increase in breaks. In the first comparable study utilizing marihuana and delta-9-THC, the results were likewise negative (93). In this study, oral doses of marihuana preparations or of delta-9-THC were administered to a group of male volunteers over a period of from 5 to 12 days. Peripheral blood leukocyte cultures were studied, and no differences were found in the number of chromosomal abnormalities between the experimental and control groups. To date it remains moot whether any one or a combination of street drugs and/or their contaminants are implicated in the production of chromosome breaks or whether these are attributable to other factors common to the experience of drug "users" as distinguished from "nonusers."

In view of the Stenchever et al. (114) findings, and those reported in another preclinical study (78), two informal conferences sponsored by NIDA's Research Division were held in August 1973 and 1974. The purpose of these meetings was to review both published and unpublished data available in this critical area. Data and experimental procedures were reviewed to weigh the most recent evidence on possible adverse effects of marihuana on chromosomes and human reproduction and to determine what additional studies in the area were warranted.

Four clinical investigators (including Dr. Stenchever) and four preclinical researchers with ongoing or completed studies in this area, participated in the first meeting. Two of the clinical investigators gave preliminary results of cytogenetic analysis performed in two different laboratories on peripheral blood samples obtained from the same marihuana users. Most of the investigators reported the results of in vivo cytogenetic analysis of peripheral blood lymphocytes. In this type of study the results of genetic damage in man can be directly observed through the light microscope. However, such examination shows only major chromosome abnormalities (i.e., breaks) which may not be the most meaningful indices of long-term effects on the population (95). While Stenchever's data showed increased rate of breakage, a study by another investigator has found negative results (92). From the other two clinical investigators, working collaboratively on the same slides, one reported a possible positive trend at one dose level while the other was completely negative. These last results are still very preliminary and were limited to a small number of subjects.

Reports from the preclinical area involving in vivo cytogenetic studies in rats showed that the effects are related to length of treatment and dose of the drug. The small number of animals treated so far precluded a conclusive finding (31). In hamsters, marihuana extract (1-100 mg/kg), LSD (0.1-1,000 µg/kg), or a combination of marihuana extract and LSD had no effect in vivo on leukocyte chromosomes from bone marrow cells, while a positive control Mitomycin produced 92 percent breaks (93).

In mice, where placental transfer is sizable, malformations of fetuses have been reported as well as detrimental effects on the reproductive process after administration of very high doses of delta-9-THC intraperitoneally (78). Some "runts" in the F1 generation were also noted after smoke administration of standardized marihuana. An earlier report by the same authors found fetus abnormalities after using contraband marihuana. These findings were not confirmed in a subsequent study (77). The preclinical data outline, once more, the importance of such experimental variables as dose, route of administration, duration of administration, etc. in the determination of drug effects.

A great deal of time was spent during both conferences discussing the various methodologies and the variations both within and between laboratories. Concern was expressed that present methodology is not precise enough to make meaningful evaluation of *unrepaired* genetic damage. In present circumstances where small differences in breakage frequencies are expected, rigorous controls must be applied to the assay to minimize the effects of extraneous variables which contribute to within subject variability when a series of pre- and posttreatment analyses are done on individual subjects. Numerous chemical, physical, and biological agents have been shown to induce chromosome breakage in human lymphocytes, both in vivo, and in vitro.

The high frequency of cells with markedly reduced numbers of chromosomes reported by Morishima (86) in three marihuana users has not been reported by others. Whether aneuploidy is more common in "users" than "nonusers" remains to be established definitively. However, aneuploidy has not been prominent in any of the previous chromosome studies of drug users. Nonetheless, as Morishima commented, since cells with such low numbers of chromosomes (5-30 instead of the normal 46) are generally regarded as technical artifacts, they may have been ignored by other investigators, and, consequently, his finding should be studied further.

Conflicting indications of a possible effect of marihuana on the cell mediated immune response have been reported (89, 110). In one of these, the cell mediated immunity of 51 chronic marihuana users as measured by in vitro lymphocyte response to allogeneic cells and to a mitogen was contrasted with that of 81 controls who have not used the drug. It was reported that a statistically significant impairment occurred comparable to that found in patients with known impairment of cellular immunity. A second study employed an in vivo skin testing procedure and a foreign antigen 2,4, dinitrochlorobenzene (DNCB) with 22 chronic marihuana users and failed to find evidence of any impairment in their cell mediated immunity. Further work in this area is being encouraged. An impairment in the immune response related to marihuana use might not only represent a potential hazard to users, but might also represent a potential therapeutic application of cannabis as an immunosuppressant and/or antitumor agent. According to two recent reports based on animal studies, marihuana has shown both types of activity (40, 71).

While there is not as yet definitive evidence that this drug represents a danger to human genetic and reproductive processes, the great importance of this question and the possible implications of some of the newer studies make it one of primary concern to be pursued very carefully in future months.

Cannabis and Psychopathology

The relationship between cannabis and psychopathology remains unresolved. There have been a number of new, uncontrolled, retrospective case reports relating cannabis use and serious mental illness (39, 60); but several well-controlled studies of large groups of cannabis users have found no statistically significant adverse effects from the drug (8, 10, 36, 38, 46). The many methodological and theoretical shortcomings of such studies are well recognized (10, 74), but at this time they offer the only information available to us.

A number of investigators have reported the results of well-controlled surveys of populations which chronically use marihuana, and all such studies were unable to demonstrate any adverse effects from chronic cannabis use. Most studies found marihuana users are not a homogeneous group (12). Beaubrun and Knight (8) and Bowman and Pihl (10) reported on chronic users in Jamaica, and Hochman and Brill (46) and Grant et al. (36) studied chronically using college undergraduates and medical students, respectively.

These reports are all described in detail in the section on Chronic Effects, above. One other such survey was conducted by Halikas et al. (37, 38) who interviewed 100 regular marihuana users and 50 nonuser friends in the St. Louis area for an assessment of possible psychopathology. The subjects were obtained through word-of-mouth chains of referrals and represented a wide range of socioeconomic and educational levels. Regular users were defined as having used marihuana at least 50 times over at least a 6-month period. The authors found that an unexpected 50 percent of each group met criteria for some psychiatric diagnosis, with one-third receiving a diagnosis of primary affective disorders. In the users, almost every diagnosed psychiatric illness began before marihuana use was initiated, and the authors concluded that "at least some regular marijuana users come from a population at high risk for psychiatric problems, and that these difficulties almost always precede use of marijuana" (37). The users did show one difference from nonusing friends, in that 12 percent received a diagnosis of sociopath compared to no such diagnosis in the control group. The shortcomings of this study are, of course, the self-selected population and the reliance upon clinical psychiatric interviews for data. The report is, however, consistent with the findings of other surveys of marihuana users.

Reports from abroad can provide accounts of experiences in populations where cannabis use is a longer standing tradition than in North America. A descriptive report of clinical observations made in Calcutta, India, at a drug addiction clinic concludes that there is a clinical condition which can be called "cannabis psychosis" (20). Two hundred cases were reviewed. Thirty-four percent of the patients, who had previously exhibited no sign of serious psychopathology, suffered an acute psychosis precipitated by a large–often first—dose of cannabis. They recovered in a matter of hours or a few days.

In patients with previously known psychopathology, Chopra and Smith (20) reported less clear findings. The role of cannabis as a trigger of psychosis was harder to pinpoint, recovery from the episode took longer, and the outcome was poorer. Like many such studies, no proper control group was included, yet the consistency and number of such reports over the years make them impossible to ignore despite limitations in the research design.

Four Jamaican males between the ages of 20 and 31 were described by Harding and Knight (39) to have a significant increase in cannabis usage following the onset of hypomanic symptoms. A well-defined manic picture developed several days after hospitalization; but at the time of admission, each patient had symptoms of schizophrenia, consisting of persecutory delusions, auditory hallucinations, withdrawal, and thought disorder. The authors conclude that heavy use of cannabis altered the expected clinical course of a manic illness by inducing a schizophreniform phase. This conclusion is unsupported by any direct evidence and, in fact, is substantially weakened by a report by Carlson and Goodwin (17) on a longitudinal study of 20 manic patients. These investigators point out that in one of three definable stages in a manic illness, schizophrenic-like symptoms—such as bizarre behavior, hallucinations, paranoia, and extreme dysphoria—commonly occur, thus giving a picture that may be difficult to distinguish from schizophrenia. The differential diagnosis rests primarily on the longitudinal course of the illness. Given this well-described common pattern of schizophreniclike episodes in mania, the role of marihuana as a causative agent must be viewed as doubtful.

Another published report casts doubt on a subject's ability to characterize his own reaction to cannabis accurately (35). In the report of "sensitivity" group behavior, experienced users said that after smoking marihuana they were happier, friendlier, warmer, and less likely to be angry or defensive. In fact, none of these factors were different whether they were in a cannabis-induced state or a placebo-induced state. While on marihuana there were no consistent affective changes, increased insights, or increased feelings of cohesiveness in the group.

In contrast to this conclusion, Salzman (107) conducted a controlled experiment using a group paradigm which obtained preliminary results showing that marihuana may reduce anger and hostility after frustration in small group settings. Subjects were measured by standard psychological tests and a modified Bales group interaction analysis. These findings are consistent with clinical observations reported by Hendin (41) of two college students in psychoanalysis who were using cannabis to manage conflicts over competition or aggression.

One of the major causes of confusion in this field, namely, the ambiguity in diagnostic classification of reported adverse psychological effects of cannabis use, is addressed in a review article by Negrete (90). A simple definition of adverse reactions is presented: "all effects which are objectively unusual, unexpected or harmful, regardless of the subjective feelings" (90); and the following diagnostic classification is proposed:

- *Severe Intoxication*—Adverse reactions caused by a simple excess of active cannabinoids, excluding any idiosyncratic, abnormal, or unusual reaction to the drug. Toxic doses of cannabis can lead to an "impaired sensorium with mild delirium, some disorientation, slurred speech and slight ataxia," and may cause psychotic states with "marked distortions in sensory perceptions, depersonalization, derealization and optical and auditory hallucinations." These reactions clear with metabolism of the active cannabinoids.
- *Pathological Intoxications*—"Intense, but short-lived adverse reactions which are emotional in nature, rather than toxic." They do not result from direct pharmacological effects of cannabis, which only acts as a precipitating agent, but are the result of personality, expectation, and setting factors. Reactions in this category would include: (a) "panic and short-lasting paranoid states with fear of police arrests and betrayal by companions, fear of death or of losing one's mind;" (b) "acute depressive states;" and (c) "severe depersonalization and derealization with consequent panic." The adverse reactions last only a few hours.
- *Acute Cannabis Psychoses*—This category includes "all those psychotic and hallucinatory conditions which follow a cannabis experience. They are usually precipitated during the cannabis intoxication . . . but remain active after the drug has been metabolized and may last as long as fifteen days." The author refers to articles in the literature which suggest that they represent only an uncovering of premorbid emotional instability or mental illness, and the belief that such reactions result from "medical mishandling of benign pathological intoxications."
- *Subacute and Chronic Cannabis Psychoses*—These are conditions described in publications from India and North Africa which are not recognized and have not yet been observed on this continent. "These conditions are described as caused by heavy, chronic consumption of the drug and have as their common clinical denominator a rather severe deterioration of the higher cognitive functions." The symptoms described are those often seen with chronic schizophrenic psychoses, and no satisfactory evidence has yet been offered to establish that what have been labeled chronic cannabis psychoses are conditions caused by direct effects of cannabis and distinct from chronic schizophrenia.
- *Residual Conditions*—These include (a) the so-called "amotivational syndrome," which may be "a reflection of attitudes consciously adopted within the frame of reference of a new philosophy of life," rather than manifestations of drug effect; and (b) echo reactions or flashbacks, which may represent increased awareness of sensations usually ignored, but initially appreciated under cannabis (90).

Although this type of classification system still has some ambiguities, it suggests an approach that, if universally adopted, would greatly help to organize the data available in the field and would give added meaning to case reports and large studies alike. In addition, establishment of a national surveillance system for recording and investigating possible adverse reactions to cannabis could be structured in accordance with these classifications.

The need for this system is highlighted by other researchers' belief that volunteer subjects underreport adverse effects of marihuana. For example, in Tart (117), a study of common marihuana experiences, reported that 21 percent of the experienced users "freaked out" one or more times. "Freaking out" was defined as an intense transient emotional upset. Twenty percent of the subjects reported at least one episode of loss of control after using cannabis and "were taken over by an outside force or will which was evil or hostile in intent" (117). Paranoid feelings were reported by 80 percent of his sample. Tart believes that even these figures are not complete, because of the tendency of marihuana enthusiasts to underreport adverse effects of the drug since such events are reported far less frequently in the usual population of volunteer subjects given marihuana in research labs (79).

Another link in the possible connection between psychopathology and adverse reactions occurring spontaneously in the real world and those seen in the research laboratory is provided by Melges et al. (81). Carefully screened normal subjects who had no detectable predisposition to delusional ideation were given hashish or alcohol so as to produce various degrees of temporal disorganization. For all subjects, as drug-induced temporal disorganization increased, so did delusionallike ideation. It should not be surprising that a person with a predisposition to delusional ideation taking a dose of cannabis in a less than optimal situation should evidence frank delusions and a "cannabis psychosis."

The finding by Melges et al. was borne out in another study on patients with prediagnosed mental illness. An experiment where THC in daily doses of 5-40 mg was given to patients with preexisting psychopathology demonstrated that such people tend to have more adverse reactions (1). A very high incidence of dysphoric reactions was noted in this group of depressed hospitalized patients undergoing a THC treatment regimen for their depression (66). These dysphoric reactions included panic, delusions, fear of dying, feelings of persecution, and other psychotic features. Seven of the 13 patients undergoing treatment experienced those symptoms to a degree. The symptoms characteristically occurred with the first dose of the drug. Patients with unipolar depressions and most deviant MMPI profiles seemed to be more likely to suffer dysphoric reactions. The incidence of such reactions to similar doses of oral THC is not usually seen in research studies with the normal volunteer subject.

Unfortunately, the role of psychopathology as a determinant is not completely unambiguous. Kotin et al. (66) believe that a lack of preparation for an experience of mood alteration and cognition may have contributed to the unpleasant response to THC in this middle-aged group of depressed patients. In experiments with normal volunteer subjects it is this very factor—lack of adequate preparation and information—that contributes to similar dysphoric reactions from cannabis (and also, interestingly enough, from LSD).

A field survey method attempted to examine the relationship between psychopathology and acute adverse reactions to LSD and cannabis in a group of 530 drug users (88). A similar pattern of adverse reactions was noted to be associated with both LSD and cannabis. Individuals with some of the characteristics of the depressed patients just discussed tended to face higher risk of adverse reactions. People skilled in the use of intellectualization, projection, and other sophisticated defenses represented in paranoid functioning seemed to face less risk. This latter group tended to be overrepresented in volunteer groups in laboratory studies, thus partially accounting for the marked difference in the incidence of adverse reactions in laboratory volunteers for cannabis studies and populations described in clinical reports or adverse studies reviewed by Marcus et al. (79).

Contradiction and ambiguity are widespread in the discussion of research to date in the relationship of cannabis and psychopathology. Further study under controlled conditions is essential before any conclusions can be accepted as fact.

References

1. Ablon, S.L., and Goodwin, F.K. High frequency of dysphoric reactions to tetrahydrocannabinol among depressed patients. *American Journal of Psychiatry*, 131:448-452, April 1974.
2. Adams, D.; MacKenzie, S.; and Loewe, S. Tetrahydrocannabinol homologs with doubly branched alkyl groups in the 3-position. *Journal of the American Chemical Society*, 70(18):668-674, 1948.
3. Adams, R.; Harfenist, M.; and Loewe, S. New analogs of tetrahydrocannabinol. *Journal of the American Chemical Society*, 71(19):1624-1628, 1949.
4. A[illegible]w, W.S., and Cassidy, J. Effect of marihuana and pla[illegible]—marihuana smoking on angina pectoris. *New Engla[illegible]urnal of Medicine*, 291:65-67, 1974.
5. Barratt, E.S.; Beaver, W.; and White, R. The effects of marijuana on human sleep patterns. *Biological Psychiatry*, 8:47-54, 1974.
6. Beaconsfield, P. Some cardiovascular effects of cannabis. *American Heart Journal*, 87:143-146, 1974.
7. Beaubrun, M.H. Drug abuse in different cultural groups in Jamaica. Presented at ANZCP/WA Meeting, Sydney, Australia, October 15-19, 1973.
8. Beaubrun, M.H., and Knight, F. Psychiatric assessment of 30 chronic users of cannabis and 30 matched controls. *American Journal of Psychiatry*, 130:309-311, March 1973.
9. Bech, P.; Rafaelsen, L.; and Rafaelsen, O. J. Cannabis and alcohol: Effect on estimation of time and distance. *Psychopharmacologia*, 30:373-381, 1973.
10. Bowman, M., and Pihl, R.O. Psychological effects of chronic heavy use. A controlled study of intellectual functioning in chronic users of high potency cannabis. *Psychopharmacologia*, 29:159-170, 1973.
11. Braucht, G.N., et al. Deviant drug use in adolescence: A review of psychosocial correlates. *Psychological Bulletin*, 79:92-106, 1973.
12. Burdsal, C.; Greenberg, G.; and Timpe, R. The relationship of marijuana usage to personality and motivational factors. *Journal of Psychology*, 85:45-51, 1973.
13. Cappell, H.D.; Kuchar, E.; and Webster, C.D. Some correlates of marijuana self-administration in man: A study of tritration of intake as a function of drug potency. *Psychopharmacologia*, 29:177-184, 1973.

14. Cappell, H.D., and Pliner, P.L. Volitional control of marijuana intoxication: A study of the ability to "come down" on command. *Journal of Abnormal Psychology*, 82:428-434, 1973.

15. Cappell, H.D., and Pliner, P.L. Regulation of self-administration of marijuana by psychological and pharmacological variables. *Psychopharmacologia*, in press, 1974.

16. Carlini, E.A., et al. Effects of marijuana in laboratory animals and in man. *British Journal of Pharmacology*, 50: 299-309, 1974.

17. Carlson, G.A., and Goodwin, F.K. The stages of mania. *Archives of General Psychiatry*, 28:221-228, 1973.

18. Casswell, S., and Marks, D.F. Cannabis and temporal disintegration in experienced and naive subjects. *Science*, 179:803-805, 1973.

19. Casswell, S., and Marks, D.F. Cannabis induced impairment of performance of a divided attention task. *Nature*, 241:60-61, January 1973.

20. Chopra, G.D., and Smith, J.W. Psychotic reactions following cannabis use in East Indians. *Archives of General Psychiatry*, 30:24-27, January 1974.

21. Cohen, M.J., and Rickles, W.H. Performance on a verbal learning task by subjects of heavy past marihuana usage. *Psychopharmacologia*, 37:323-330, 1974.

22. Cohen, S. Principal investigator. UCLA, NIMH contract HSM-42-71-89.

23 Cousens, K., and DiMascio, A. Delta-9-THC as an hypnotic: An experimental study of three dose levels. *Psychopharmacologia*, 33:355-364, 1973.

24. Darley, C.F., et al. Marihuana and retrieval from short-term memory. *Psychopharmacologia* (Berlin), 29:231-238, 1973.

25. Darley, C.F., et al. The nature of storage deficits and state dependent retrieval under marijuana. *Psychopharmacologia*, 37:139-149, 1974.

26. Darley, C.F., et al. Influence of marihuana on storage and retrieval processes in memory. *Memory and Cognition*, 1:196-200, 1973.

27. Davis, J.P., and Ramsey, H.H. Antiepileptic action of marihuana-active substances. *Federation Proceedings*, 8:284-285, 1949.

28. Dittrich, A., Battig, K.; and Zeppelin, I. Effects of delta-9-tetrahydrocannabinol on memory, attention and subjective state. *Psychopharmacologia*, 33:369-376, 1973.

29. Domino, E.F.; Rennick, P.; and Pearl, J.H. Dose-effect relations of marijuana smoking on various physiologic parameters in experienced male users—observations on limits of selftitration of smoke. *Clinical Pharmacology and Therapeutics*, 15:514-520, 1974.

30. Editorial: Cannabis and the cardiovascular system, *Journal of the American Medical Association*, 225(1):58, 1973.

31. Epstein, S., and LaVappa, K. Mutagenicity testing of marihuana. 1973, to be published.

32. Fairbairn, J.W., et al. Cannabinoid content of some English reefers, *Nature*, 249:276-278, May 1974.

33. Feinberg, I., et al. Effects of chronic high dosage delta-9-tetrahydrocannabinol (THC) on sleep patterns in man. Submitted for publication September 1974.

34. Freemon, R.F. The effect of delta-9-tetrahydrocannabinol on sleep. *Psychopharmacologia*, in press.

35. Galanter, M., et al. Marihuana and social behavior—a controlled study. *Archives of General Psychiatry*, 30:518-521, April 1974.

36. Grant, I., et al. A neuropsychological assessment of the effects of moderate marihuana use. *Journal of Nervous and Mental Disease*, 156:278-280, April 1973.

37. Halikas, J.A.; Goodwin, D.W.; and Guze, S.B. Marihuana effects—a survey of regular users. *Journal of the American Medical Association*, 217:692-694, 1971.

38. Halikas, J.A.. Goodwin, D.W.; and Guze, S.B. Marihuana use and psychiatric illness. *Archives of General Psychiatry*, 27:162-165, 1972.

39. Harding, T., and Knight, F. Marihuana-modified mania. *Archives of General Psychiatry*, 29:635-637, November 1973.

40. Harris, L.S., et al. Retardation of tumor growth by delta-9-THC. *Pharmacologist*, 16:259, 1974.

41. Hendin, H. Marihuana abuse among college students. *Journal of Nervous and Mental Disease*, 156:259-270, April 1973.

42. Hill, S.Y., et al. Marijuana: CNS depressant or excitant? *American Journal of Psychiatry*, 131:313-315, 1974.

43. Hill, S.Y., et al. Marijuana and pain. *Journal of Pharmacology and Experimental Therapeutics*, 188:415-418, 1974.

44. Hill, S.Y., et al. State dependent effects of marijuana on human memory. *Nature*, 243:241-242, May 1973.

45. Himmelsbach, C.K, Treatment of the morphine-abstinence syndrome with a synthetic cannabis-like compound. *Southern Medical Journal*, 37:26, 1944.

46. Hochman, J.S., and Brill, N.Q. Chronic marihuana use and psycho-social adaptation. *American Journal of Psychiatry*, 130:132-140, February 1973.

47. Hollister, L.E. Cannabidiol and cannabinol in man. *Experientia*, 29:825, 1973.

48. Hollister, L.E. Interactions in man of delta-9-tetrahydrocannabinol, I. Alphamethylparatyrosine. *Clinical Pharmacology and Therapeutics*, 15:18-21, January 1974.

49. Hollister, L.E. Structure-activity relationships in man of cannabis constituents and homologs and metabolites of delta-9-tetrahydrocannabinol. *Pharmacology*, 11:3-11, 1974.

50. Hollister, L.E., and Gillespie, H.K. Delta-8- and delta-9-tetrahydrocannabinol. *Clinical Pharmacology and Therapeutics*, 14(3):353-357, May-June 1973.

51. Hollister, L.E., et al. Marihuana metabolites in urine of man. *Clinical Pharmacology and Therapeutics*, 13(6):849-855, November-December 1972.

52. Hollister, L.E., and Reaven, G.M. Delta-9-tetrahydrocannabinol and glucose tolerance. *Clinical Pharmacology and Therapeutics*, 16:297-302, 1974.

53. Hollister, L.E.; Richards, R.K.; and Gillespie, H.K. Comparison of tetrahydrocannabinol and synhexyl in man. *Clinical Pharmacology and Therapeutics*, 9:783, 1968.

54. Hollister, L.E., and Tinklenberg, J.R. Subchronic doses of marihuana extract. *Psychopharmacologia*, 29:247-252, 1973.

55. Hosko, M.J.; Kochar, M.S.; and Wang, R.I.H. Effects of orally administered delta-9-tetrahydrocannabinol in man. *Clinical Pharmacology and Therapeutics*, 14(3):344-352, May-June, 1973.

56. Isbell, H., et al. Effects of delta-9-trans-tetrahydrocannabinol in man. *Psychopharmacologia*, 11:184, 1967.

57. Jones, R.T. Contract #HSM4273181.

58. Karniol, I.G., and Carlini, E.A. Comparative studies in man and in laboratory animals on delta-8- and delta-9-trans-tetrahydrocannabinol. *Pharmacology*, 9:115-126, 1973.

59. Kielholz, P. et al. An experimental investigation about the effect of cannabis on car driving behavior. *Pharmakopsychiatrie Neuro-Psychopharmakologie*, 6:91-103, 1973.

60. Klepfisz, A., and Racy, J. Homicide and LSD. *Journal of the American Medical Association*, 223(4):429-430, 1973.

61. Klonhoff, H. Marihuana and driving in real-life situations. *Science*, 186:317, October 25, 1974.

62. Klonhoff, H.; Low, M.; and Marcus, A. Neuropsychological effects of marijuana. *Canadian Medical Association Journal*, 108:150-156, January 1973.

63. Kochar, M.S., and Hosko, M.J. Electrocardiographic effects of marihuana. *Journal of the American Medical Association*, 225(1):25-27, July 1973.

64. Kolodny, R.C., et al. Depression of plasma testosterone levels after chronic intensive marijuana use. *New England Journal of Medicine*, 290:872-874, April 1974.

65. Kopell, B.S.; Tinklenberg, J.R.; and Hollister, L.E. Contingent negative variation amplitudes. *Archives of General Psychiatry*, 27:809-811, December 1972.

66. Kotin, J.; Post, R.M.; and Goodwin, F.K. Delta-9-tetrahydrocannabinol in depressed patients. *Archives of General Psychiatry*, 28:345-348, March 1973.

67. LeDain, G., et al. *Cannabis: A Report of the Commission*

of Inquiry into the Non-Medical Use of Drugs. Information, Ottawa, Canada, 1972.

68. Lemberger, L., et al. Comparative pharmacology of delta-9-tetrahydrocannabinol and its metabolite, 11-OH-delta-9-tetrahydrocannabinol. *The Journal of Clinical Investigation*, 52:2411-2417, October 1973.

69. Lemberger, L., et al. The pharmacologic effects and physiologic disposition of delta-6a, 10a demethylheptyl tetrahydrocannabinol (DMHP) in man, to be published.

70. Lemberger, L. Tetrahydrocannabinol metabolism in man. *Drug Metabolism and Disposition*, 1(1):461-468, 1973.

71. Levy, J.A., et al. Effects of delta-8- and delta-9-THC on the immune response in mice. *Pharmacologist*, 16:259, 1974.

72. Lewis, E.G., et al. The effects of varying doses of delta-9-tetrahydrocannabinol on human visual and somatosensory evoked response. *Electroencephalography and Clinical Neurophysiology*, 35:347-354, 1973.

73. Linnoila, M. Effect of drugs and alcohol on psychomotor skills related to driving. *Annals of Clinical Research*, 6:7-18, 1974.

74. Linton, P.H.; Kuechenmeister, C.A.; and White, H.B. Marijuana and performance: A psychophysiological study of tasks and evoked responses in man. *American Journal of Psychiatry*, in press.

75. Lopez, H.H., et al. Cannabis—accidental peroral intoxication. *Journal of the American Medical Association*, 227: 1041-1042, March 1974.

76. Low, M.D.; Klonoff, H.; and Marcus, A. The neurophysiological basis of the marijuana experience. *Canadian Medical Association Journal*, 108:157-165, January 1973.

77. Lynch, V. Marihuana research: Teratogenetic and pharmacogenetic aspects, to be published.

78. Mantilla-Plata, B.; Clewe, G.L.; and Harbison, R.D. Teratogenic and metagenic studies of delta-9-tetrahydrocannabinol in mice. *Federation Proceedings*, 32(3):746, Abstract No. 2995, 1973.

79. Marcus, A.M.; Klonoff, H.; and Low, M. Psychiatric status of the marihuana user. *Canadian Psychiatric Association Journal*, 19:31-39, February 1974.

80. Mechoulam, R., et al. Chemical basis for hashish activity. *Science*, 169:611-612, 1970.

81. Melges, F.T., et al. Temporal disorganization and delusionallike ideation. *Archives of General Psychiatry*, 30:855-861, June 1974.

82. Mendelson, J.H. *Behavioral and Biological Concomitants of Chronic Marihuana Use*. Final Report Contract DADA 17-73-C-3082 from the Department of the Army to the Alcohol and Drug Abuse Research Center, McLean Hospital, Belmont, Massachusetts, September 23, 1974.

83. Mendelson, J.H., and Meyer, R.E. Quoted in: Marihuana: the grass may no longer be greener. *Science*, 185:683-685, August 1974.

84. Messiha, F.S., and Soskin, R.A. Effect of *Cannabis sativa* administered by smoking on biogenic amine excretion in man. *Research Communications in Chemical Pathology and Pharmacology*, 6(1):325-328, July 1973.

85. Meyer, R.E., and Mendelson, J.H. *Cited in Marihuana: A Signal of Misunderstanding*. First Report of the National Commission on Marihuana and Drug Abuse. Washington, D.C.: U.S. Government Printing Office, 1972.

86. Morishima, A. Testimony before U.S. Senate Committee on the Judiciary Subcommittee on Internal Security, May 16, 1974.

87. Moskowitz, H.; S[illegible]za, R.; and Burns, M. Effect of marihuana on the psychological refractory period. *Perceptual and Motor Skills*, 38:959-962, 1974.

88. Naditch, M.P. Acute adverse reactions to psychoactive drugs, drug usage and psychopathology. *Journal of Abnormal Psychology*, 83:394-403, 1974.

89. Nahas, et al. Inhibition of cellular mediated immunity in marihuana smokers. *Science*, 183:419, 1974.

90. Negrete, J.C. Psychological adverse effects of cannabis smoking: A tentative classification. *Canadian Medical Association Journal*, 108:195-196, January 1973.

91. Neu, R.L., et al. Delta-8- and delta-9-tetrahydrocannabinol: Effects on culture human leucocytes. *Journal of Clinical Pharmacology*, 10(4):228-230, July-August 1970.

92. Nichols, W.W. Personal communication.

93. Nichols, W.W., et al. Cytogenic studies on human subjects receiving marihuana and delta-9-THC. Mutation Research, 26:413-417, 1974.

94. Nicholson, M.T.; Pace, H.B.; and Davis, W.M. Effects of marihuana and lysergic acid diethylamide on leucocyte chromosomes of the golden hamster. Submitted to *Chemical Pathology and Pharmacology*.

95. Nowell, P.C. Biological significance of induced human chromosome aberrations. *Federation Proceedings*, 28(6): 1797-1802, 1969.

96. Parker, C.S., and Wrigley, F. Synthetic cannabis preparations in psychiatry. I. Synhexyl. *Journal of Mental Science*, 96:276, 1950.

97. Pearl, J.H.; Domino, E.F.; and Rennick, P. Short term effects of marijuana smoking on cognitive behavior in experienced male users. *Psychopharmacologia*, 31:13-24, 1973.

98. Perez-Reyes, M., et al. Pharmacology of orally administered delta-9-tetrahydrocannabinol and its monohydro-hydroxylated metabolites in man. *Experientia*, 29(8)1009-1010, August 15, 1973.

99. Perez-Reyes, M.; Timmons, M.C.; and Wall, M.E. Long term use of marihuana and the development of tolerance or sensitivity to delta-9-tetrahydrocannabinol. *Archives of General Psychiatry*, 31:89-91, July 1974.

100. Quarles, W.; Ellman, G.; and Jones, R. Toxicology of marijuana: Conditions for conversion of cannabidiol to THC upon smoking. *Clinical Toxicology*, 6:211-216, 1973.

101. Rafaelsen, O.J., et al. Cannabis and alcohol: Effects on simulated car driving. *Science*, 179-920-923, March 1973.

102. Rafaelsen, L., et al. Effects of cannabis and alcohol on psychological tests. *Nature* 242:117-118, March 1973.

103. Renault, P.F., et al. Repeat administration of marihuana smoke to humans. *Archives of General Psychiatry*, 31:95-102, July 1974.

104. Rickles, W.H.; Cohen, M.J.; and Naimark, R.S. Marihuana and physiological reactivity to stress. Paper presented at the Annual Meeting of the American Psychiatric Association in Honolulu, Hawaii, May 1973.

105. Rickles, W.H., et al. Marijuana induced state dependent verbal learning. *Psychopharmacologia*, 30:349-354, 1973.

106. Roth, W.T., et al. Electrocardiographic monitoring during marihuana intoxication. *Clinical Pharmacology and Therapeutics*, 14:533-540, July-August 1973.

107. Salzman, C. *Study of the Effect of Marijuana on Hostility in a Group Setting*. NIMH Grant DA 00519-01, #RO3. April 1, 1973-March 31, 1974. Personal communication.

108. Schwin, R., et al. Marihuana and critical flicker fusion. *Journal of Nervous and Mental Disease*, 158:142-144, 1974.

109. Sidell, F.R., et al. Dimethylheptyl-delta-6a-10a-tetrahydrocannabinol: Effects after parenteral administration to man (37134). *Proceedings of the Society of Experimental Biological Medicine*, 142:867-873, 1973.

110. Silverstein, M., and Lessin, P. Normal skin responses in chronic marijuana users. *Science*, in press.

111. Spector, M. Acute vestibular effects of marijuana. *The Journal of Clinical Pharmacology*, 13(5-6):214-217, May-June 1973.

112. Spector, M. Chronic vestibular and auditory effects of marijuana. *Laryngoscope*, 84:816-820, May 1974.

113. Stenchever, M.A., and Allen, M. The effect of delta-t-tetrahydrocannabinol on the chromosomes of human lymphocytes *in vitro*. *American Journal of Obstetrics and Gynecology*, 114:821, 1972.

114. Stenchever, M.A.; Kunysz, T. J.; and Allen, M.A. Chromosome breakage in users of marihuana. *American Journal of Obstetrics and Gynecology*, in press. Also reported in *Hospital Tribune*, April 16, 1973.

115. Stillman, R.C.; Weingartner, H.; and Wyatt, R.J. State-dependent effects of marijuana. *Proceedings of the 80th Annual Convention of the American Psychiatric Association*, 1972.

116. Stillman, R.C., et al. State-dependent (dissociative) effects of marihuana on human memory. *Archives of General Psychiatry*, 31:81-85, July 1974.

117. Tart, C.T. Marihuana intoxication: common experiences. *Nature*, 226:701-704, 1970.

118. Tashkin, D.P.; Shapiro, B.J.; and Frank, I.M. Acute pulmonary physiologic effects of smoked marijuana and oral delta-9-tetrahydrocannabinol in healthy young men. *New England Journal of Medicine*, 289(7):336-341, August 1973.

119. Thompson, L.J., and Proctor, R.C. Continued use of pyrahexyl in treatment of alcoholic and drug withdrawal conditions. *North Carolina Medical Journal*, 14:520, 1953.

120. Tinklenberg, J.R., et al. Marihuana and alcohol. *Archives of General Psychiatry*, 27:812-815, 1972.

121. Vachon, L., et al. Single-dose effects of marihuana smoke. Bronchial dynamics and respiratory-center sensitivity in normal subjects. *New England Journal of Medicine*, 288: 985-989, May 1973.

122. Valk, L.E.M. Hemp in connection with opthalmology. *Opthalmologica*, 167:413-421, 1973.

123. Volavka, J., et al. EEG, heart rate and mood change ("high") after cannabis. *Psychopharmacologia* (Berlin), 32:11-25, 1973.

124. Weingartner, H., et al. Effect of marihuana and synthetic delta-9-THC on information processing. *Proceedings of the 80th Annual Convention of the American Psychiatric Association*, 813-814, 1972.

125. Wendkos, M.H. Electrocardiographic effects of marihuana. *Journal of the American Medical Association*. 226:789-790, November 1973.

126. Widman, M. et al. Plasma protein binding of 7-hydroxy-delta-1-tetrahydrocannabinol: An active 1-tetrahydrocannabinol metabolite. *Journal of Pharmacy and Pharmacology*, 25:453-457, June 1973.

127. Zalcman, S., et al. Marijuana and amphetamine: The question of interaction. *American Journal of Psychiatry*, 130: 707-708, June 1973.

128. Zeidenberg, P., et al. Effect of oral administration of delta-9-tetrahydrocannabinol on memory, speech, and perception of thermal stimulation results with four normal human volunteer subjects. Preliminary report. *Comprehensive Psychiatry*, 14:549-556, 1973.

5 Therapeutic Aspects

In many parts of the world cannabis has been, and is still, used as a folk medicine. The second *Marihuana and Health Report* contained a review of the early uses. The modern phase of therapeutic use of cannabis began about 140 years ago when O'Shaughnessy (17) reported on its effectiveness as an analgesic and anticonvulsant. At about the same time Moreau de Tours (16) described its use in melancholia and other psychiatric illnesses. Those who saw favorable results observed that cannabis produced sleep, enhanced appetite, and did not cause physical addiction. It was tried in the treatment of opiate addiction, chronic alcoholism, the delirium tremens, and a wide variety of painful disorders.

Some troublesome drawbacks have historically accompanied therapeutic trials of cannabis. Its content of delta-9-tetrahydrocannabinol (delta-9-THC) was highly variable—even active preparations gradually lost potency while standing on pharmacy shelves. The gastrointestinal absorption of the active ingredients was delayed and uncertain because of their inability to dissolve easily. Therefore, when aspirin, barbiturates, and other synthetic analgesics and sedatives became available, the medical use of extract of *Cannabis indica* faded. The Marihuana Tax Act of 1937 was the final blow, which eliminated it from medical practice.

During the past decade delta-9-THC has been synthesized, and supplies have been made available to investigators. Laboratory tests for the detection of cannabinoids in body fluids have been refined. Precisely assayed marihuana which maintains its delta-9-THC content fairly well under favorable storage conditions is now supplied to investigators by the National Institute on Drug Abuse (NIDA). These advances, plus public and scientific interest in the nature of marihuana effects in man, have generated renewed activity in the therapeutic potential of this substance. Over 35 active preclinical and clinical studies concerning the therapeutic aspects of cannabis compounds are being performed in North America at present. In addition, water soluble analogues of delta-9-THC are being investigated for possible usefulness. Although most of the reports are clearly preliminary, uncontrolled studies, they are summarized here because they represent advanced techniques in the evaluation of a therapeutic agent like cannabis. The cannabinoid molecular structure is unique to medicine, and it deserves examination and exploration for potential usefulness.

Analgesia

Several reports, including those collected by the Indian Hemp Commission, allege that marihuana relieves pain. Two recent preclinical investigations tend to confirm the impression. Kaymakcalan et al. (14) intravenously administered 1 mg/kg of delta-9-THC to dogs. Pain thresholds were measured by electrical stimulation of electrodes implanted into a tooth. The pain threshold increased fourfold, and a definite analgesia was obtained. However, tolerance to the analgesic, sedative, and atactic effects developed after 8 days. These authors had previously reported analgesia to delta-9-THC in mice and rats as measured by the tail flick and writhing tests, and in rabbits by sciatic nerve stimulation. In the doses used, analgesia was equivalent to that provided by morphine. In rats a cross-tolerance between delta-9-THC and morphine was noted. A second study (18) measured the antinociceptive effect of delta-9-THC on rats using electrical intracranial stimulation and escape response tests. A nondose-related increase in pain thresholds as well as an attenuation in the escape response was observed. Some of the animal work measuring pain thresholds is questioned because hypnotic doses were employed which masked the response to pain.

Hill et al. (12), working with human subjects, found that pain thresholds decreased, rather than increased, with the administration of marihuana. She gave 26 male subjects either 12 mg of delta-9-THC from marihuana containing 1.4 percent

THC or a marihuana placebo cigarette. The pain threshold was determined by the verbal response to ascending or descending levels of electrical stimulation to the skin. The heightened sensitivity to a painful sensory signal is consistent with reports of "perceptual sharpening" from marihuana. Pain thresholds are only one factor in pain perception, and other variables such as attention will have to be measured.

Anticonvulsant Effects

The effects of THC congeners on five retarded children whose grand mal epilepsy had been poorly controlled with the conventional medications of diphenylhydantoin and phenobarbital were studied (7). The THC-like compounds worked as well or better than these drugs in all children, according to the investigators.

Several preclinical studies have been undertaken during the past several years in an effort to study the effects of delta-9-THC on audiogenic, electrical, or pentylentetrazol (Metrazol) induced seizures. Recently Consroe and Man (4, 5) tested delta-8- and delta-9-THC on all three seizure models. Both compounds had a dose-related blocking effect on the audiogenic maximal electroshock and maximal pentylentetrazol-induced seizures. The significance of the results can be evaluated by a comparison with those obtained with diphenylhydantoin using the same models. Both diphenylhydantoin and the THC compounds have a similar qualitative spectrum of anticonvulsant activity. Boggan (1) has tested delta-9-THC on audiogenic seizure-susceptible mice and has reported that it is an effective anticonvulsant.

The anticonvulsant properties of some natural cannabis compounds on rat hippocampal seizures precipitated by sequences of afferent electrical stimulation were measured in another study of the anticonvulsant effects of cannabis compounds (13). The investigators found the cannabis compounds to be effective in decreasing susceptibility to hippocampal seizure discharges when administered intraperitoneally or topically. By weight the cannabis compounds were more active than either diphenylhydantoin or mysoline. Cannabidiol was the most potent agent with cannabinol, delta-9-THC, and delta-8-THC following in decreasing order of effectiveness.

Sedative, Hypnotic, and Anesthetic Aspects

The quieting effects of marihuana were among those first noted. The hypnosedative action was seen at dosages which appeared to have little toxicity. There has been some interest in testing the drug as a sleeping medication. Cousens and DiMascio (6) gave either a placebo or 10, 20, or 30 mg of delta-9-THC orally in double-blind fashion to nine mild insomniacs. The tests were conducted once per week for 6 weeks in an incomplete Latin Square. The results showed that THC effectively decreased the time required to fall asleep. According to this study, delta-9-THC has a hypnotic action of short duration. During the presleep phase the side effects were those of mood alteration and temporal disintegration. After waking, some subjects had a "hangover," some had a "high." A few had residuals of the temporal disintegration, the duration of which was dose related.

Freemon et al. (8) demonstrated that after the oral administration of 20 mg delta-9-THC at bedtime to five volunteers, a decrease in REM stage sleep occurred. This finding confirms REM time reduction reported in other studies. After four-to-six consecutive nights of administration of the drug, it was abruptly stopped. The sudden withdrawal was followed by mild insomnia, but a marked REM rebound was not observed during the withdrawal phase. The role of cannabis in the treatment of insomnia remains to be determined.

Several studies have reported on the interaction of THC with barbiturates. Sofia (24, 25) has shown that the pretreatment of mice with delta-9-THC decreases the sedative dose required and increases the duration of sleeping time of nine commonly used sedative hypnotics.

From recent preclinical investigations (20, 26, 31), delta-9-THC would seem to increase the effectiveness of anesthetics. In two studies (20, 26) the impact of delta-9-THC upon the minimal alveolar concentrations of cyclopropane and halothane was assessed. Delta-9-THC produced a dose-related reduction of minimal alveolar concentrations of both anesthetics. The implication is that less of the anesthetic was needed. Smith (23) gave delta-9-THC to normal human subjects in order to study its anesthetic or preanesthetic potential. Following the intravenous injection of a maximum dose of 200 mg/kg, marked sedation with minimal respiratory depression was observed. Other physiologic effects noted were: decreased salivation, a modest bronchodilation, and an increased cardiac output primarily on the basis of a dose-related tachycardia. The investigator cautions that certain of the observed effects may have been due to the alcohol in which the delta-9-THC was dissolved. If these preliminary impressions can be confirmed—namely, that marked sedation is accompanied by a lack of respiratory depression—there may be some potential usefulness for delta-9-THC as an adjunct to anesthesia.

Antidepressant Effect

Because of its well-known euphoriant quality, marihuana has been used to treat depressions in the past, and investigations of thi[illegible]tential use are currently under way. Kotin [illegible] (15) gave eight hospitalized, depressed pa[illegible]3 mg/kg of delta-9-THC or a placebo twi[illegible]daily under double-blind conditions for at least 1 week. Placebos were also administered during the week before and following the THC week. All patients had been diagnosed as having a primary affective disorder by two psychiatrists and a social worker. The degree of depression was considered either moderate or severe. No evidence of a significant mood elevating and antidepressant effect was discerned. Longer periods of testing the drug would appear desirable in chronic depressive states.

Bronchodilator Effects

During the past 2 years two studies have indicated that marihuana is a potent bronchodilator in human subjects. Vachon et al. (30) tested the effects of single doses of marihuana on bronchial dynamics. Seventeen normal, nonnaive subjects were used, of whom nine smoked 2.6 percent and eight smoked marihuana containing 1.0 percent delta-9-THC. All subjects received a comprehensive baseline battery of pulmonary function tests. Physiologic variables were measured prior to and at 2, 6, and 20 minutes after smoking. Airway resistance decreased significantly in the high-dose group. Reciprocally, specific airway conductance and mean expiratory flow rates at 25 percent of vital capacity increased significantly. The low-dose group had similar changes.

Tashkin et al. (27), using 32 healthy, hospitalized nonnaive subjects, did a double-blind study in which random assignments to a placebo marihuana group, a 1 percent delta-9-THC group, and a 2 percent delta-9-THC group were made. They also found that specific airway conductance increased, and airway resistance decreased. The peak pulmonary effects occurred at 15 minutes and were still present at 60 minutes. In a subsequent study this group achieved response curves in increases of specific airway conductance when 0, 10, 15, and 20 mg of oral delta-9-THC were employed. Peak effects following oral administration were recorded at 3 hours, and some effects persisted for 6 hours. Tashkin and his group (28) also compared marihuana with inhaled isoproterenol—a beta adrenergic stimulant—commonly used in treating bronchial asthma. They produced eight episodes of acute bronchospasm with methacholine in 10 stabilized asthmatics. During other study sessions bronchospasm was induced by exercise. Isoproterenol or its placebo and a 500 mg marihuana cigarette containing 2 percent delta-9-THC or its placebo were administered. Bronchospasm was promptly reversed by isoproterenol and cannabis but not by the placebos. The bronchodilator effect of smoked marihuana is not due to beta adrenergic stimulation according to these findings (29). Current data from the Tashkin group indicate that delta-9-THC does not act on the basis of inhibition of the muscarinic receptors.

In contrast to the above studies, Schwin (22) reported no significant changes in tidal volume in 15 subjects who smoked 1.5 percent delta-9-THC containing marihuana as compared to a group of 31 normals. He states that this measurement of pulmonary function is ordinarily increased by bronchodilating agents. This, therefore, suggests that marihuana has little usefulness in the treatment of asthma.

Other findings from the Tashkin group indicate that chronic, heavy smoking of marihuana causes mild but significant respiratory functional impairment, affecting both smaller and larger airways. However, individual doses of the drug in those who are not persistent, heavy users may still have a positive bronchodilating effect (29). The fact that marihuana increases the diameter of bronchi in a manner unlike that of standard antiasthmatic agents makes its further investigation desirable.

Intraocular Pressure

In 1971 Hepler and Frank (9) reported that normal subjects sustained a drop in intraocular pressure following the smoking of marihuana containing 1 or 2 percent delta-9-THC. This finding has been confirmed by other investigators. Hepler (10) has started a program of treating patients with ocular hypertension or glaucoma, particularly those whose intraocular pressure is not reduced with conventional medications for this purpose. He is also exposing rabbits to marihuana smoke and to topical applications of delta-9-THC to try to determine how it works on ocular hypotension.

Green and Pederson (11) conducted studies on the secretion and filtration of the isolated rabbit ciliary body and on the aqueous dynamics in vivo. They had found that after application of delta-9-THC to the ciliary body in vitro, fluid secretion was reduced and passive permeability was increased. Following intravenous THC administration into the rabbit, they noted a decrease in intraocular pressure, a 60-70 percent increase in total facility and a 100 percent increase in protein formation. They suggest that the action of marihuana may be due to a reduction in ciliary capillary pressure causing decreased formation of fluid. They also state that "Vasoconstriction could also cause an increase in aqueous outflow, since aqueous and blood compete for the same episcleral outflow vessels" (11).

A preliminary clinical report attributes several clinically desirable effects to the therapeutic use of delta-9-THC with a sample of 34 cancer patients. The data collected thus far suggest that the drug is an appetite stimulant which helps retard weight loss in this group as well as having anti-emetic and analgesic qualities. It was also felt that the drug served as a tranquilizer and mood elevator. The drug was administered by a double-blind technique. This group also reports that the patients receiving THC did not experience the usual intoxicant effect sought by street users of cannabis. They attribute this to the difference in set and the lack of preconceptions on the part of these patients (21).

Mechanism of Action

Marihuana, delta-9-THC, and other cannabinoids appear to have a broad spectrum of possible therapeutic effects. To date no clear explanation of the mechanism of action for any of these effects exists. However, Burstein et al. (2, 3) have proposed that the pharmacological action of the delta-9-THC may be due to inhibition of prostaglandin biosynthesis. Prostaglandin, PGE_2, PGE, and PGF all have a wide range of pharmacologic actions on all organ systems. Prostaglandins have been shown to increase intraocular pressure and to cause bronchoconstriction. Several studies have concluded that the analgesic effects of aspirin and of Indomethacin are on the basis of prostaglandin inhibition. The possibility that cannabis actions may be mediated by the alteration of the availability of prostaglandins at certain sites in the body must be considered.

Marihuana, despite its current controversial status, is worth further investigation for therapeutic efficacy. The ED_{50}:LD_{50} ratio is extremely favorable. Toxicity is low in therapeutic amounts; the potential for physical dependence is negligible, although psychological dependence is certainly a possibility. Some of the preliminary studies are promising enough to make additional work worthwhile. On the negative side, its psychoactive effects are sometimes undesirable, tolerance may develop with consistent use, and the dose-related rapid pulse rate is a drawback. However, related compounds may eliminate some of the drawbacks. At any rate, further research is needed both in the areas mentioned above and in new fields before definitive statements can be made.

References

1. Boggan, W.O.; Steele, R.A.; and Freedman, D.X. Delta-9-tetrahydrocannabinol effect on audiogenic seizures susceptibility. *Psychopharmacologia,* 29(2):101-106, 1973.
2. Burstein, S., and Raz, A. Inhibition of prostaglandin E_2 biosynthesis by delta-1-tetrahydrocannabinol. *Prostaglandins,* 2(5):369-374, November 1972.
3. Burstein, S.; Levin, E.; and Varanelli, C. Prostaglandins and cannabis-II, inhibition of biosynthesis by the naturally occurring cannabinoids. *Biochemical Pharmacology,* 22(22):2905-2910, November 1973.
4. Consroe, P.F., and Man, D.P. Effects of delta-8- and delta-9-tetrahydrocannabinol on experimentally induced seizures. *Life Sciences,* 13(5):429-439, September 1973.
5. Consroe, P.F., et al. Letter: Reduction of audiogenic seizure by delta-8- and delta-9-tetrahydrocannabinols, *Journal of Pharmacy and Pharmacology,* 25(9):764-765, September 1973.
6. Cousens, K., and DiMascio, A. Delta-9-THC as an hypnotic: An experimental study of three dose levels. *Psychopharmacologia,* 33:355-364, 1973.
7. Davis, J.A., and Ramsey, H.D. Antiepileptic action of marihuana active substance. *Federation Proceedings,* 8:284-285, 1949.
8. Freemon, F.R. The effect of delta-9-tetrahydrocannabinol on sleep. *Psychopharmacologia,* 35:39-44, 1974.
9. Hepler, R.S., and Frank, I.R. Marihuana smoking and intraocular pressure. *Journal of the American Medical Association,* 217(10):1932, September 10, 1971.
10. Hepler, R.S. Personal communication.
11. Green, K., and Pederson, J.E. Effect of delta-1-tetrahydrocannabinol on aqueous dynamics and ciliary body permeability in the rabbit. *Experimental Eye Research,* 15:499-507, 1973.
12. Hill, S.Y., et al. Marihuana and pain. *Journal of Pharmacy and Experimental Therapeutics,* 188:415-418, 1974.
13. Izquierdo, I., and Orsingher, O.A. Effect of cannabidiol and of other *Cannabis sativa* compounds on hippocampal seizure discharges. *Psychopharmacologia,* (Berlin) 28(1):95-102, 1973.
14. Kaymakcalan, S.; Turker, K.; and Turker, M. Analgesic effect of delta-9-tetrahydrocannabinol and development of tolerance to this effect in the dog. *Psychopharmacologia,* 35:123-128, 1974.

15. Kotin, J.; Post, R.M.; and Goodwin, F.K. Delta-9-tetrahydrocannabinol in depressed patients. *Archives of General Psychiatry*, 28:345-348, March 1973.

16. Moreau de Tours, J. Psychotic depression with stupor: tendency toward dementia: treatment with an extract of *Cannabis indica*. *Lancette Hospital Gazette*, 30:391, 1857.

17. O'Shaughnessy, W.B. On the preparation of the Indian hemp or gunjah. *Translations of Medicine, Physiology and Sociology*, Bengal: 1838-1840, pp. 71-102; 1842, pp. 421-461.

18. Parker, J.M., and Lubas, T.C. Automatic determination of the pain threshold to electroshock and the effects of delta-9-THC. *International Journal of Clinical Pharmacology, Therapy and Toxicology*, 7(1):75-81, February, 1973.

19. Pars, H.G. The other side of marihuana research. *The Journal of Anesthesiology*, 36:519-520, June 1973.

20. Paton, W.D.M., and Temple, D.M. Effects of chronic and acute cannabis treatment upon thiopentone anesthesia in rabbits. *Proceedings of the British Pharmacological Society*, January 4-7, 1973.

21. Regelson, W., et al. Personal communication to Dr. Thaddeus J. Domanski, National Cancer Institute. Awards Review, Bethesda, Maryland. Re: Renewal and Continuation of Grant for Virginia Commonwealth University, Medical College of Virginia, An Acute and Chronic Behavioral Toxicity Study of Delta-9-THC in Cancer Patients. July 1, 1974.

22. Schwin, R. Marihuana and tidal volume. *Journal of the American Medical Association*, 223(2):194-195, January 8, 1973.

23. Smith, T. Personal communication.

24. Sofia, R.D., and Knobloch, L.C. The interaction of delta-9-tetrahydrocannabinol pretreatment with various sedative-hypnotic drugs. *Psychopharmacologia*, (Berlin) 30(2):185-194, 1973.

25. Sofia, R.D. Interactions of chronic and acute delta-1-tetrahydrocannabinol pretreatment with zoxazolamine and barbiturates. *Research Communication in Chemical Pathology and Pharmacology*, 5(1):91-97, January 1973.

26. Stoelting, R.K., et al. Effects of delta-9-tetrahydrocannabinol on halothane MAC in dogs. *Anesthesiology*, 38(6):521-523, June 1973.

27. Tashkin, D.P.; Shapiro, B.J.; and Frank, I.M. Acute pulmonary physiologic effects of smoked marijuana and oral delta-9-tetrahydrocannabinol in healthy young men. *New England Journal of Medicine*, 289(7):336-341, August 16, 1973.

28. Tashkin, D.P.; Shapiro, B.J.; and Frank, I.M. Acute effects of smoked marihuana and oral mechanism of increased specific airway delta-9-tetrahydrocannabinol on specific airway conductance in asthmatic subjects. *American Review of Respiratory Discussions*, 109:420, 1974.

29. Tashkin, D.P. Personal communication.

30. Vachon, K., et al. Single dose effect of marihuana smoke. *New England Journal of Medicine*, 288(19):985-989, May 10, 1973.

31. Vitez, T.S., et al. Effects of delta-9-tetrahydrocannabinol on cyclopropane MAC in the rat. *Anesthesiology*, 38(6):525-527, June 1973.

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